Volume XXI Number 3

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

MARCH
1960

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DISEASES *of the* Nervous System

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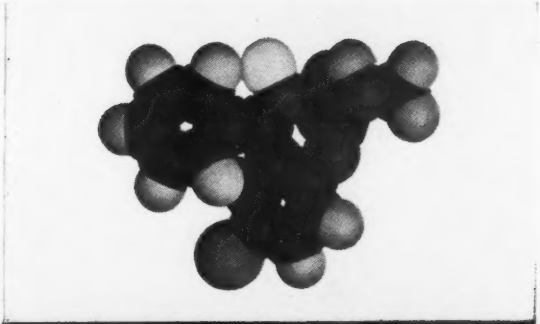

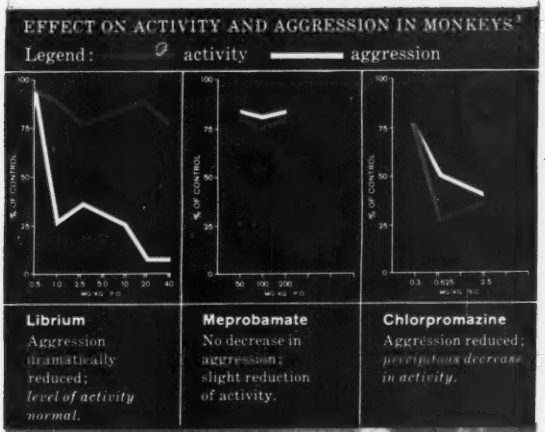

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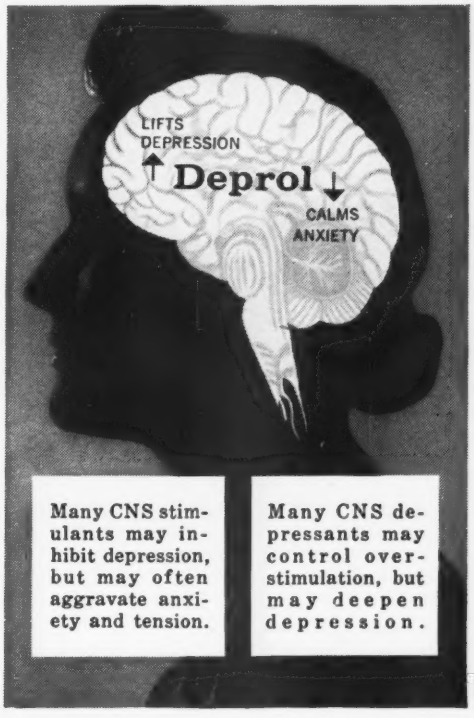
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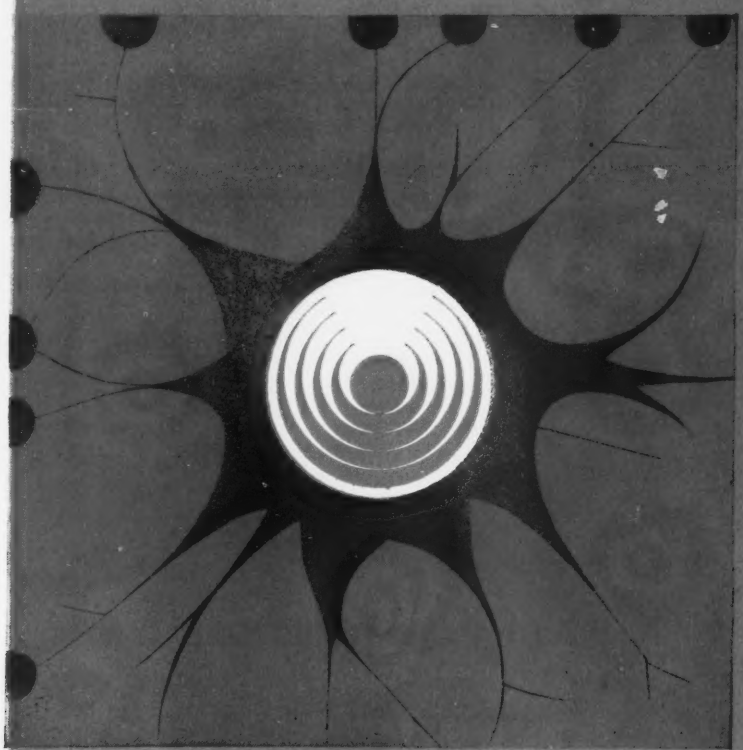

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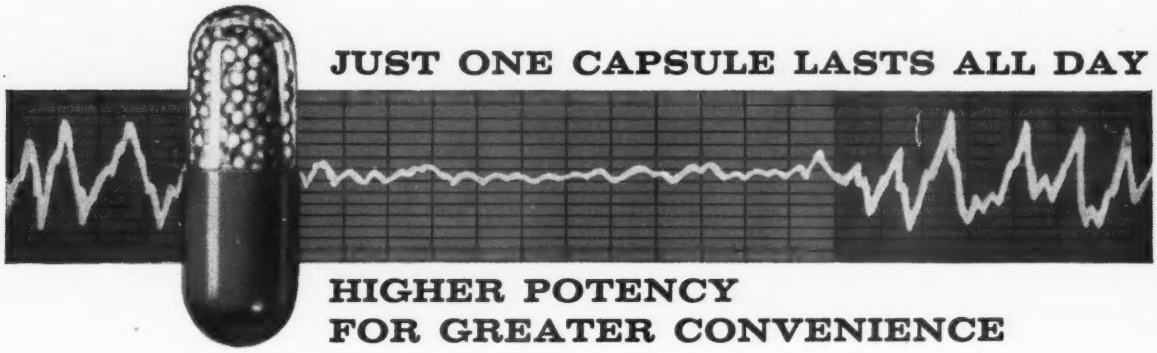

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Volume XXI MARCH 1960 Number 3

DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Effect of Schizophrenic Plasma Upon Original Learning in the Rat

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M. P. BISHOP

Introduction

Experiments thus far reported which have investigated possible "psychotoxic" effects of injections of schizophrenic serum or plasma in rats have failed generally to demonstrate such effects. Recent research in this area appears to have been prompted by the taraxein studies of Heath and his coworkers[1,2] at Tulane, the reported failures of other investigators[3,4,5] to confirm Heath's findings (independent confirmatory evidence[6,7,8] has subsequently been published), and the possibility that these failures to replicate the Tulane results might be attributable to difficulties in processing schizophrenic serum to obtain the taraxein fraction. Utilization of a small laboratory animal such as the white rat allows injection of raw serum or plasma, thus circumventing the fractionation procedures, and also, of course, provides opportunity for employment of more rigid laboratory controls than are possible in research with human subjects.

Winter and Flataker[9,10] trained rats to climb a rope for a food reward and then measured the effects of intraperitoneal injections of psychotic (mostly schizophrenic) plasma versus normal plasma on the speed of this rope-climbing response. For animals injected with psychotic plasma, they reported a highly signicant decrement in rope-climbing performance and observed that these animals appeared generally sluggish and less active than the normal-plasma-injected controls. These results were interpreted as suggesting a "psychotoxic factor" in the psychotic plasma. Equation of motor retardation with a genuine psychotoxic effect seems questionable, and even the conclusion of impaired motor performance (which was certainly justified by the data) appears possibly attributable to artifact in view of the failure of other investigators to confirm these findings.

Kety[11] reports an unpublished study by Kornetsky which failed to demonstrate differential effects of schizophrenic and normal plasma on the rope-climbing task. Ghent and Freedman[12] directly replicated the Winter and Flataker experiment and found significant motor impairment following injection of either schizophrenic or normal plasma, with no difference between these in magnitude of effect. Stern *et al.*,[13] identifying general activity level as a probable basic component of the rope-climbing performance, studied the effects of injections of schizophrenic plasma, normal plasma and saline on two measures of activity: open-field behavior and activity-wheel running. Again, no differential effect of schizophrenic and normal plasma was found for either of these types of activity, but both schizophrenic and normal plasma produced a significant reduction of running in the activity wheel.

It appears probable that other attempts to demonstrate psychotoxic effects of schizophrenic plasma in the rat have been made, but have not reached publication because of failure to obtain positive findings. The author is aware of one such effort by Anger, of the Upjohn research laboratories, to demonstrate influence of schizophrenic serum upon the performance of a trained bar-pressing response which at last report had resulted in "no satisfactory conclusions."[14]

From Psychological Services, Tulane Training and Research Unit, East Louisiana State Hospital, Jackson, Louisiana.

This research was supported in part by a grant from the Division of Training and Research, Louisiana Department of Hospitals.

Rationale of the Present Study

The author wondered whether reported failures to demonstrate a psychotoxic effect of schizophrenic plasma in rats might be explained in terms of the type of behavior which has been investigated. The typical procedure employed in studies to date has involved extensive pre-training of animals on some relatively simple task (bar-pressing, rope-climbing) prior to plasma injections. This procedure, of course, does not test the effect of injections upon learning, but rather upon the performance of an already over-learned response. Clinical judgement suggests that this choice of highly over-learned responses may have been an inappropriate one. Despite the hazards of generalizing from human behavior to rat behavior, it seemed reasonable to the author to employ a method which would allow adverse effects upon rat behavior more nearly analogous to the difficulties which the schizophrenic patient experiences (and which are presumably attributable to the disturbing effects of the hypothesized psychotoxic agent). While theories as to the nature of schizophrenia certainly do not lack diversity, some sort of "adaptational breakdown," i.e., impairment of ability to adapt successfully to a variety of life situations, is generally recognized as a manifestation of this disease. This inability to learn new adaptive responses, especially under conditions of stress, lends itself quite readily to research at the animal level and would appear to provide a more appropriate test of possible psychotoxic effects of schizophrenic plasma in animals than have the "over-learned response" techniques thus far employed. Even the deteriorated back-ward schizophrenic typically retains the ability to perform simple highly-over-learned motor responses (e. g., lighting a cigarette). At any rate, these over-learned "reflexive-type" responses appear minimally impaired relative to impairment of capacity for new adaptive learning. If we make the admittedly shaky assumption that the posited toxic substance in schizophrenic blood might affect the CNS of the rat in essentially the same way that it affects the CNS of man, a significant decrement in the performance of a highly over-learned response as a function of injection of schizophrenic plasma could not be reasonably predicted.

For the present investigation of effects of schizophrenic plasma upon original adaptive learning, an instrumental avoidance learning task was selected. Specifically, the task employed here requires that the rat learn to jump a barrier in response to a buzzer in order to avoid an electric shock to the feet. Such a task demands adaptive learning under inherently stressful conditions. In addition, if the duration of delay between onset of CS (buzzer) and of UCS (shock) is fairly long and latency of response is not used as a criterion measure, this technique prevents confounding of motor impairment with true learning decrement.

Summary Statement of the Problem

This experiment was designed to study the effects of intraperitoneal injections of schizophrenic versus normal plasma upon original learning (specifically, the acquisition of an avoidance response) in the albino rat. The method used differed in one significant respect from other studies of this type previously reported. No pre-training of any sort was employed, and the animals faced the original adaptive learning task under the influence of the plasma (or control saline).

In a second phase of the experiment, animals which had successfully learned the avoidance task were given additional training trials to produce over-learning, and were then injected and tested for impairment in performance of the avoidance response. This approximates a replication of the rope-climbing and bar-pressing studies, and provides an opportunity for comparison of effects of injection upon original learning versus over-learned-response performance under identical laboratory conditions.

The study, in essence, was designed to test the following hypotheses:

1. Injections of schizophrenic plasma will produce significant impairment of original learning.

   (a) On an avoidance learning task, group results for animals injected with schizophrenic plasma will be significantly poorer than results for those injected with plasma from normal controls or with a placebo (saline).

(b) Results for the "normal" and "saline" groups will not differ significantly.

2. In the retention of an *over-learned* avoidance response, results for animals injected with schizophrenic plasma will be poorer than for those injected with plasma from normal controls or with a placebo.

(An alpha level of .05 was established for the testing of all hypotheses.)

Procedure

Animal Subjects: 65 male and female albino rats; Sprague-Dawley strain. All animals were within the range of 175-225 grams. No special gentling or handling was employed, and none of the animals had been previously used in other experiments.

Human Subjects (Blood Donors):

Chronic Schizophrenics: 25 (12 males; 13 female) chronic schizophrenic patients who were randomly selected from a group of 50 such patients displaying clear-cut schizophrenic symptoms who had been intensively screened by the author and three psychiatrists (faculty consultants from the Department of Psychiatry and Neurology, Tulane University School of Medicine) to rule out physical disease, mental deficiency, organic brain damage, or other possibly contaminating variables. All had been off medication of any kind for a minimum of two months prior to being used for the study, except for Unicap vitamin capsules which each had received daily for the past two years. These patients have been housed in a special research unit (Tulane Training and Research Unit, East Louisiana State Hospital, Jackson, Louisiana) for the past 30 months, during which time they have received excellent physical care, regular exercise, and a diet equal in nutritive value to that of the hospital employees serving as normal controls.

Normal Controls: 20 (9 males; 11 female) hospital employee volunteers, who were roughly equated with the patient group as regards age, absence of physical disease, and educational and socioeconomic levels. Volunteers were not screened psychologically or psychiatrically to rule out possible underlying schizophrenic defect. They are "normals" as defined by gainful employment and reasonably adequate social and occupational adjustment.

Table I summarizes descriptive data for the normal and schizophrenic groups.

Apparatus: As shown in Figure 1, apparatus consisted of a Warner-type "shuttle-box" with two separately chargeable grids divided by a barrier which is charged when either grid is charged. Shock is delivered via a combination of a "powerstat" variable transformer and a current-limiting variable resister. A buzzer mounted on the control box provides the CS. Operation is manual. A Standard S1 timer (not shown) was added for the second portion of the study to allow measurement of response latencies.

Method

This study utilized a simple randomized groups design with 65 animals and 45 hu-

TABLE I

Descriptive Data for Normal and Schizophrenic Blood Donors

	Normal	Schiz.*
Age (yrs.)		
Mean	34.4	37.2
S.D.	11.3	6.8
Range	18–57	26–49
Education (yrs.)		
Mean	10.6	11.2
S.D.	2.5	2.2
Range	6–16	7–17
Length of Hosp. (yrs.)		
Mean	—	10.2
S.D.	—	5.3
Range	—	5–23
No. of Subjects	20	25

*Most of these patients would now probably be classified as "chronic undifferentiated." Diagnosis based upon earlier predominant symptoms breaks down as follows: Catatonic—13; Paranoid—6; Hebephrenic—4; Undifferentiated—2.

Figure 1. Avoidance Learning Apparatus.

man subjects from whom individual blood samples were obtained. Animals were randomly divided into three groups with Ns equal to those of the two human-subject groups plus an additional control group of 20 animals which received injections of saline. In other words, each animal in groups other than the saline group served as a representative of a particular human subject, i.e., was injected with plasma from this subject and faced the avoidance learning task under the influence of this injection. Fresh heparinized plasma was used in all cases. The procedure for obtaining blood samples and for processing these to obtain heparinized plasma was identical for all human subjects. The procedure for injecting and running the rats was identical for all animals.

It was possible to run only three animals per day on the original avoidance learning task. Animals were caged in groups of three, and cage-mates were used as subjects on any given experimental day. (Typically, one of these received normal plasma, another schizophrenic plasma, and the third saline.) Although no food reward was employed, animals were maintained on a 20-hour food deprivation schedule to insure that they would be alert and active at the time of testing. Water was *ad lib.*

Blood samples were drawn immediately prior to lunch, with donors fasting at least four hours, and the blood was centrifuged to obtain individual samples of heparinized plasma. These were immediately refrigerated, and were brought to lab room temperature (70°-80°) before injection. Approximately five hours prior to injection, the three animals which were to be used that night were placed together in the apparatus and allowed to explore it for a period of 30 minutes. This was the extent of preliminary habituation. At 7:00, 7:15 and 7:30 P.M. respectively, the three animals received intraperitoneal injections (1 cc. per 100 grams body weight—about 2 cc.) and were caged alone following injection. Animals were then trained continuously, one after the other, on the avoidance learning task with 20-trial runs beginning at the following number of minutes after injection for each: 45, 90, 130, 160, and continuing if necessary at 30-minute intervals until the criterion of six consecutive avoidance responses was reached. Each run was preceded by an adaptation period (60 seconds on first run; 30 seconds thereafter) followed by presentation of the buzzer CS. Shock UCS was delivered after three seconds if the animal failed to jump the barrier, and was continued along with the buzzer until the animal escaped to the safe compartment. Buzzer, or buzzer and shock, were terminated when the rat crossed the barrier. A modification of the diminished interval conditioning procedure was used. On run #1 the average inter-trial interval was 30 seconds; on run #2 it was 20 seconds; and thereafter it was 15 seconds.

An arbitrary cut-off was established at 140 trials. Any animal failing to reach criterion in seven runs was terminated and assigned a trials-to-criterion score of 140. Animals which were able to learn the task within the 140-trial limit were terminated as soon as they reached the learning criterion.

The above applies to the original avoidance learning procedure which was the crucial portion of this study and provided data for the testing of the major hypothesis. To test hypothesis #2, a procedure was used which is essentially a replication (with a different task) of earlier studies, some of which have reported positive findings which seem possibly artifactual. Two groups of 20 animals each, randomly selected from those which had successfully completed the avoidance learning procedure, were retrained on this task to a criterion of 10 successive correct responses to produce *over-learning.* One of these groups received injections of normal plasma and the other schizophrenic plasma. (The 20 schizophrenic donors were randomly selected from the original 25 patients.) Immediately prior to injection, each animal received 10 additional trials in the apparatus. Response latencies and number of correct responses for these pre-injection trials were recorded. The animal was then injected intraperitoneally (1 cc. per 100 grams) and caged alone. One hour following injection, it was returned to the apparatus and given 20 test trials. Latencies and total correct responses were again recorded. This technique provided a measure of the

effects of the two types of plasma upon retention of this over-learned avoidance response (comparison of per cent correct responses before and after injection for each group) and also a measure of motor-impairment *per se* (which should be reflected in longer response latencies following injection).

Although not essential to the testing of stated hypotheses, an additional measure of "activity level" or "emotionality" under conditions of schizophrenic versus normal plasma or saline injections was also employed. This was a simple emergence test, i.e., a measure of the time required for an animal to emerge from its cage onto an attached platform once the cage was opened. Scheduling limitations required that this test be run on a separate group of animals from those used in the avoidance learning procedure. Sixty additional naive animals were divided into three groups of 20. One group received injections of schizophrenic plasma, another normal plasma and the third saline, in dosages as before. Each animal was caged alone for a period of 24 hours before testing. One hour prior to testing it was removed, quickly injected, and returned immediately to its cage. The test consisted simply of opening the drawer-type cage, attaching the platform and measuring the time required for the animal to emerge from the cage and place all feet on the platform. An arbitrary 10-minute limit was employed.

Results

Original Avoidance Learning: Results for the original avoidance learning task clearly supported the prediction that animals injected with schizophrenic plasma would show significant impairment of learning as compared with animals injected with normal plasma or saline. Table II presents the comparative data for the three groups.

TABLE II

Summary Data for Original Avoidance Learning

	Plasma		
	Saline	Normal	Schiz.
No. of Animals	20	20	25
Median Trials to Criterion	73.0	73.5	140.0
No. of Rats which Learned	16	17	12
Per Cent	80%	85%	48%
No. Rats Failing to Learn	4	3	13
Per Cent	20%	15%	52%

Because of the abnormal distribution of trials-to-criterion scores imposed by the arbitrary cut-off at 140 trials, statistical analysis was restricted to a simple "Learned/Failed to Learn" dichotomy, with chi square comparisons between groups. The "saline" versus "schizophrenic" comparison yields a chi square of 4.84 with $P<.03$. For the "schizophrenic" versus "normal" groups, chi square $= 6.64$ with $P<.01$. The difference between the "saline" and "normal" groups is obviously not significant. If results for both the normal and saline control groups are combined and contrasted with the data for the schizophrenic group, the resulting chi square $= 8.60$, which is significant at the .005 level.

Comparison of median correct response for the various groups on successive blocks of learning trials demonstrates a rather striking difference in rate of learning for the animals injected with schizophrenic plasma as compared with the normal plasma and saline-injected animals. As is shown in Figure 2, the average animal in the "normal" and "saline" groups shows rapid acquisition of the avoidance response, whereas the typical animal in the "schizophrenic" group shows an extremely poor rate of learning. (The grouped data indicate an apparent spurt upward on the last block of trials. This was more than four hours after injection and suggests that effects of the plasma were possibly wearing off.)

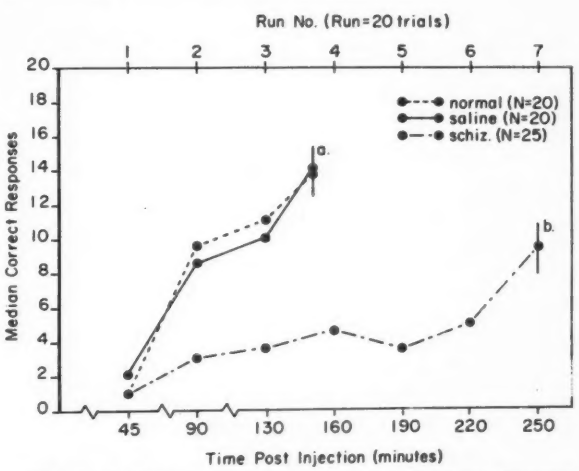

Figure 2. Rate of Learning for the Various Groups on the Avoidance Task.

a. Median animal in Normal and Saline groups had learned task.

b. Median animal in Schizophrenic group had not yet learned task.

Retention of the Over-Learned Avoidance Response: Hypothesis #2 predicted no differential effects of schizophrenic and normal plasma injections on the performance of a highly over-learned avoidance response. As noted earlier, this phase of the study constitutes a methodological replication of several earlier studies, except that in this case the response studied was conditioned barrier-jumping rather than rope-climbing or bar-pressing. Comparative results for animals injected with normal plasma and those injected with schizophrenic plasma are presented in Table III. Neither type of plasma produced significant impairment of performance. None of the small differences observed, either between groups or between pre-injection and post-injection results within groups, is statistically significant.

The response latency data are particularly interesting. (Latency here is the time between onset of the buzzer and the animal's crossing the barrier on each successful avoidance response.) It was felt that this measure should reveal any influence of plasma injections upon motor performance which might exist independently of influence upon "mental" functioning in the rat. No motor retardation was found for either group as can be seen by comparison of pre-injection and post-injection mean latency scores. This finding appears contrary not only to the rope-climbing results of Winter and Flataker and to the data on activity-wheel running reported by Stern et al. (in which both schizophrenic and normal plasma produced marked reduction in activity), but also to the results of the present study for cage emergence, presented below. A probable explanation of these apparently conflicting data will be considered in the discussion section.

TABLE III

Summary Data for Retention of the Over-Learned Avoidance Response

	Normal Plasma	Schiz. Plasma
No. of Animals	20	20
Correct Responses (Per Cent):		
Pre-injection	85.0%	82.0%
Post-injection	84.5%	87.5%
Response Latencies:		
Pre-injection		
Mean (sec.)	1.26	1.28
S.D. "	0.62	0.60
Post-injection		
Mean (sec.)	1.25	1.30
S.D. "	0.58	0.63

Emergence Test: To provide an additional measure of effects of plasma injections upon "activity level" or "emotionality," three supplementary groups of 20 animals each were injected with 2 cc. normal plasma, schizophrenic plasma and saline, respectively, and each animal was scored for the latency of its emergence from its cage onto an attached platform one hour after injection. In both the schizophrenic and normal-plasma injected groups, 9 of the 20 animals failed to emerge from their cages within the 10-minute limit imposed. In the saline injected group, only one animal of the 20 failed to emerge. A simple contingency table comparing data for the "saline" group versus either the "schizophrenic" or "normal" groups yields a chi square of 8.53 which is significant at the .005 level. Obviously, the "schizophrenic" and "normal" groups did not differ, but each showed highly significant retardation as compared with the saline-injected animals.

Median emergence times for the various groups were as follows: Saline—176 seconds; normal plasma—494 seconds; schizophrenic plasma—542 seconds. The difference in median latency between the normal and schizophrenic plasma groups may be attributed to chance. A "median test for two samples"[15] applied to these scores yields a chi square of 1.01 which is definitely not significant. Whatever the explanation for this retarded emergence behavior (motor impairment, fearfulness, lowered motivation?), the retardation appears to be produced in equal degree by either schizophrenic or normal plasma, and is apparently independent of the influence of schizophrenic plasma upon learning ability which was demonstrated in the first portion of this study.

Discussion

Results of this experiment clearly confirm the stated hypotheses that schizophrenic plasma injected intraperitoneally in rats will produce significant impairment of original avoidance learning; that impairment of learning is not produced by injections of

normal plasma; and that no such differential effects of schizophrenic and normal plasma are observed if the animals have received extensive pre-training or opportunity for over-learning of the response prior to plasma injection. More simply, there appears to be some substance in the blood plasma of chronic schizophrenic patients which is capable (in the rat) of interfering with new learning, but has no demonstrable effect upon the performance of an already well-learned response. This is, of course, a generalization from the specific type of learning involved in this study to learning in general, and may have to be revised as future data become available. It is, nevertheless, an interesting finding and accords well with the clinical observations which prompted the original hypotheses. It is felt that this detrimental effect of schizophrenic plasma upon learning ability (especially in the absence of differential effects of schizophrenic and normal plasma upon all other behavior measured in this study) provides fairly good evidence of a genuinely psychotoxic substance in schizophrenic blood, and definitely supports, at the animal level, Heath's taraxein findings in humans.

Control of Possible Contaminating Variables: In an area of research in which conflicting reports have become almost the rule rather than the exception, it is the responsibility of the investigator, as Kety[11] has stressed, to discuss possible sources of error in his data and interpretation of findings. In this regard, it should be pointed out immediately that this study as it stands offers no conclusive evidence that the demonstrated psychotoxic property is *specific to schizophrenia.* The difference between normals and schizophrenics appears clear-cut, but the possibility remains that the toxic substance may be a product of metabolic changes produced by the severe or prolonged stress common to many diseases. The data reported here are actually incomplete. The original design calls for the testing of plasma samples from three additional groups: acute schizophrenics, non-schizophrenic NP disorders, and chronic physical diseases. These studies are currently in progress, but data are not sufficient to report on as yet. Inclusion of these additional groups should throw light on the specificity problem and provide answers to many questions relating to possible alternative explanations of the psychotoxic effects of schizophrenic plasma.

With regard to the schizophrenic versus normal comparison, it is felt that experimental controls were better than those which can usually be applied in studies of this sort. The author was fortunate in having access to a group of chronic schizophrenic patients ideally suited for research of this type. Because these patients have been maintained in a biochemically oriented research facility for more than two years, every effort has been made during that time to minimize extraneous variables which might cause these patients to show spurious divergence from the norm on various biochemical measures.

The author has had close contact with this group of schizophrenic patients and with the employee group used as normal controls for a period of more than two years, and feels especially confident that results of this study could not have been influenced by diet. The superiority of meals served to patients in this particular facility over those served in the remainder of the hospital (including the employees' dining room) is a source of frequent complaint among the employees. With the long-term supplementary vitamin therapy which has been employed, the diet of the schizophrenic group would appear certainly equal to that of the controls.

"Schizophrenia" is considered by some to be a collective label for a group of different disorders which happen to have some symptoms in common. The author's own bias is toward the view that schizophrenia is a single disease, that it is a joint product of genetic and psychological factors, with the genetic factor(s) determining a metabolic abnormality which underlies the basic "integrative defect" and lowered stress tolerance, and the psychological factors (stresses of infinite variety) interacting with the metabolic deficiency to produce the varied clinical pictures observed. This view assumes that the clinical variability is explainable primarily in terms of the varied psychological pressures, and that the basic biochemical disturbance is qualitatively similar (but varies quantitatively) from patient to patient. Until biases are supplanted by evidence,

however, the possibility of diverse disorders under a common label must be considered. This consideration suggests that results be analysed in terms of individual as well as group values. Unfortunately, the present data do not lend themselves to this sort of analysis. Variability among individual animals on an avoidance learning task is quite high. This variability makes it impossible to determine how any given animal might have performed in the absence of injection, and we must depend upon statistical treatment of grouped data for our conclusions. It should be noted, however, that, despite clearly divergent group results, there was overlapping between groups. Thirty-two per cent of animals in the schizophrenic group achieved trials-to-criterion scores superior to the median for the normal-injected group. The plasma samples in these cases apparently did not produce a marked toxic effect, but whether they produced a mild effect or none at all cannot be determined. Certainly, some variability both in the toxicity of the plasma and in resistance of the animals to this toxin would be expected. Intraperitoneal absorption times are also variable and it is possible that some animals injected with schizophrenic plasma were "bright" enough to master the task before sufficient toxin to impair learning was absorbed.

The likelihood of examiner bias influencing the results in this sort of animal study is minimal, but a check on this was provided by the use of coded samples. Roughly half of the plasma samples used in the original learning phase of the study and all samples used in other portions of the study were coded. Learning data from the coded and uncoded samples did not differ. (The author was quite unsuccessful, incidentally, in an attempt to identify type of plasma injection by observing the cage behavior of the animals following injection for the emergence test.)

It has already been noted that all patients used in this study had been off medication for a minimum of 60 days. Actually, all but three had been off for 90 days. This, along with the absence of differential effects of schizophrenic and normal plasma upon general behavior or responsiveness, makes it extremely unlikely that the present findings could have been influenced in any way by residual effects of medication. Kety[11] raises the additional possibility that varied therapies to which the chronic schizophrenic patient has been exposed might result in permanent metabolic changes. Such a possibility could more easily account for differential laboratory biochemical findings between schizophrenics and normals than for the rather specific and predicted behavioral abnormality produced in this study by injections of schizophrenic plasma. The current extension of this research to include acute untreated schizophrenics should provide more definitive evidence on this point.

It should be stressed that results of this study in no way bear upon the genetic-biochemical versus psychogenic controversy regarding the *etiology* of schizophrenia. The author's bias on this issue has already been acknowledged, but the ultimate solution of the "Which came first?" question has hardly been hastened by this experiment.

Relation of Motor Retardation to Type of Task:

It was noted in the preceding section that the plasma injections failed, in the overlearned avoidance response task, to affect speed of response. The emergence test, on the other hand, demonstrated marked reduction in activity following injection of either schizophrenic or normal plasma. Stern *et al.*[13] have reported similarly conflicting results, their animals showing marked reduction in activity-wheel running after either type of injection, but no decrement in performance in an "open-field" apparatus. The explanation of these results may lie in the rather peculiar physical reaction which is produced in the rat by intraperitoneal injection of human plasma from whatever source. Winter and Flataker[9] mentioned the "powerful abdominal contractions" produced by an "occasional plasma sample." With the dosages of about 2 cc. used in the present study, a noticeable effect of this sort was observed in all plasma-injected animals. The reaction does appear to involve abdominal contractions, but also includes an apparent ataxia of the hind legs and generalized sluggishness. This effect is usually noticeable within

three or four minutes after injection and may last from about half an hour to several hours. In some animals it is mild, in others quite severe. Observed in their cages, many animals at the height of this reaction appear almost totally incapacitated; they cannot walk without flopping to one side and may occasionally be found lying on the floor of the cage in an apparent stupor. Surprisingly, however, this condition is almost instantaneonsly reversible if the animal is alerted in any way (e.g., by a sharp tap on the cage), placed in unfamiliar surroundings, or generally subjected to stress of any sort. When placed in the shuttle-box apparatus, for example, the effect seems to disappear entirely and the plasma-injected animals cannot be differentiated from those injected with saline. This combination of sluggishness and motor impairment, which is transiently reversible under conditions of stress, can probably account for the conflicting results which have been obtained with various measures of activity level or response speed. Tasks involving an element of stress (Stern's open field test and the avoidance task in this study) fail to demonstrate motor retardation; non-stressful measures of spontaneous activity (Stern's activity-wheel running and the present emergence test) reveal significant impairment of activity with either schizophrenic or normal plasma.

Summary

Effects of intraperitoneal injections of schizophrenic plasma, normal plasma and saline were studied in rats. Hypotheses, derived by generalization from a judged impairment of adaptive learning in the schizophrenic disorder to adaptive learning at the animal level, predicted detrimental effects of schizophrenic plasma upon "new learning" as opposed to "old learning" in the rat. Specifically, it was predicted that: (1) injections of schizophrenic plasma would produce significant impairment of original learning in an avoidance learning task, and that such an effect would not be produced by injections of normal plasma; (2) no significant difference in performance between normal-plasma-injected animals and schizophrenic-plasma-injected animals would be shown if the animals had received extensive pre-training on the test task prior to injection. The technique employed in the testing of the latter hypothesis was methodologically similar to that used in earlier studies which have reported conflicting results.[9,10,12,13]

Findings confirmed both hypotheses. For original avoidance learning, grouped data show no differential effects of normal plasma and saline injections, but a highly significant impairment of learning in rats injected with plasma from chronic schizophrenic patients. In the retention of an already *over-learned* avoidance response, animals injected with schizophrenic plasma did not differ (either in per cent correct responses or in speed of response) from those injected with normal plasma. Data were interpreted as demonstrating a psychotoxic effect of schizophrenic plasma in the rat and as supporting Heath's taraxein findings in humans.

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Hypnosis and Medical Practice

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Hypnosis, referred to by a different term, was utilized in ancient times as evidenced by historical references in various ceremonies. Primitive cultures in religious rites induced a trance in participants by the rhythmic beat of drums and chants. The laying on of hands or religious objects or merely waving the arms over the body, by legend, gave supernatural powers to the individual. The participant's body could be tortured by cuts, lashes and burns without sensitivity. Mud or herbal dyes were rubbed in the cuts. This, too, gave no subjective pain at the time nor thereafter, even though usually the wounds would become badly infected. These wounds formed keloids, decorative to the minds of fellow tribesmen and tribeswomen. In some tribes this denoted manhood and eligibility for marriage. Other tribes used it only for decorations and still others for a mark of bravery or hunting prowess. Even today these ceremonies are practiced in many parts of the world, notably in Africa and Australia.

The ancient Greeks and Egyptians and Oriental cultures are known to have used hypnotic phenomena in their societies. Their medicine men and mystics used it to drive out demons from diseased bodies. The American Indian's witch doctor by suggestion cured many trying ills. Even today we know that if left alone many of our patients would improve.

The modern history of hypnosis begins about 1770 with Mesmer, who reputedly attended demonstrations of fantastic healing powers by Father Gassner. Father Gassner claimed that he was driving demons out of the body but Mesmer did not adhere to this concept. Dr. Mesmer began utilizing what he termed "animal magnetism" and he believed that, just as a magnet had a field flowing between the two poles, so the body circulated an invisible magnetic fluid. Disease, he believed, was due to improper flow of this fluid. He utilized any fluid that he had magnetized as the medium for trance induction. He was discredited by doctors in Vienna and moved to Paris where a French commission was appointed to investigate his methods and render an official verdict. Our own Benjamin Franklin was on this French commission. Needless to say, they found him guilty and he was discredited in France. He moved to England for a few years under an assumed name and later returned to Austria to die in poverty and obscurity in 1815. Mesmer had assistants and students in his various practices, however, who used and developed Mesmer's theories, changing them as they continued making more critical observations. Lafayette and one Puysegur (who first noted and described the deep trance and called it somnambulism) Charcot, Babinski and several others believed in this magnetism and carried on some work in this area. It became known as "mesmerism" after Mesmer.

Braid, a Scotch physician in England, coined the word "hypnosis," meaning sleep-like. It is said that the first modern operation under hypnotic anesthesia was done by the French doctor, Recamier, in 1821. Cloquet in 1829 reported his use of this form of anesthesia in surgery. Elliotson, an Englishman, performed many experiments in hypnosis and recorded them in 1843. Dr. James Esdaile, an Englishman of the magnetic school, utilizing hypnosis, performed over 3000 operations in Calcutta, India, and published his works in book form in 1850. He utilized many assistants who were taught to blow upon the eyes and move hands slowly over the patients for hours in inducing trance state for surgical operations. There was no effective anesthetic for use in surgery. The patient would be strapped down and the operation performed, or he could go into a trance and lose awareness of the pain. As chemical anesthesia was not yet known, the patient was glad to accept the procedure, and needless to say, Esdaile became medically omnipotent to many in India. Hypnosis in Europe during these years was becoming a medical tool for such men as Charcot, Bernheim (who first discovered that the trance was due to suggestion), Forel, Kraft-Ebing, Brewer, Moll, Sperling, Des-

soir, Kraepelin, Von Schrenk-Notzing, Pavlov, Wetterstrand, Felkin, Bramwell, Lloyd, Tuke, Tuckey and others.

Dr. Sigmund Freud, the founder of the dynamic theory of human behavior, and a brilliant psychiatrist noted the world over, used hypnosis but gave it up for long term therapy. Because of his definite, over-all rejection of hypnosis, he set the study and use of this scientific tool back many years. I feel that he was a poor hypnotist and should have rejected it for himself only, instead of flatly rejecting it for all medical use.

In Europe various showmen put on elaborate public demonstrations which have lead to laws in most all European nations prohibiting its use for entertainment. This outlawing of the use of hypnosis for entertainment would be welcomed by the medical profession in the United States.

In America the first surgery known to be done under hypnosis was performed by Wheeler, to remove a nasal polyp. The patient was hypnotized by Mr. Quimby, a magnetizer. Quimbly also treated Mary Baker Eddy in 1862 for a neurotic condition. She later disagreed with the suggestion theories of hypnosis and added her religious faith concept in the founding of the Christian Science sect. A teaching of Christian Scientists is to warn all adherents to stay away from hypnosis and medicine and rely only on religious faith.

Other forms of hypnosis prevalent in this country are yogi, dianetics, progressive relaxation, and even natural childbirth. The psychophysiological phenomena called hypnosis all but dropped out of medical use due to Freud's influence until World War I. On occasion during the war, hypnosis was shown to be dramatically effective, and Hall of Yale University began running controlled experiments in his laboratory to further clarify the phenomena. World War II stimulated interest further in hypnosis and its use has grown steadily in the United States and throughout the world. Hypnosis in medicine has for many years been approved formally by medical groups in Europe and elsewhere. The American Medical Association approved its use in American medicine September 1958. This A.M.A. approval has stimulated a marked interest in the procedure.

There is a broad opportunity for hypnosis in general practice as well as in medical specialties including psychiatry and psychological sciences. As doctors, we use levels of hypnosis in our every day practice, knowingly or otherwise. We do this by giving many suggestions to patients. "Mrs. Brown, I think you will improve rapidly if you take these tablets four times a day," is a simple example. We have learned not to infer that we don't think the medication will help. The suggestion is implied, by giving the prescription, that you have confidence in its curative powers. It often may be observed that the white aspirin compound is not as helpful for some patients as the pink or green one given previously. Suggestion and receptivity of the patient were stronger when you gave the first prescription.

Hypnosis is a normal psychological state of being unconsciously attentive to suggestion and ideas. In the use of hypnosis we present ideas that the patient can use to help himself to accomplish a goal. If the suggestion is not compatible with the personality of the patient, he will not accept it. There is no more danger in hypnosis than in any other form of interpersonal relationship of comparable intensity. The doctor learns a great deal about his patients, and to have a good practice is to have good interpersonal relationships with patients. The doctor has prestige with the patients and therefore his advice is highly acceptable. With hypnosis they consider the advice and the suggestions even more willingly and deeply. It may be asked, "Will the patient accept hypnosis in treatment?" If the patient has a need and is willing to cooperate, he will accept it. Even if the patient is afraid of hypnosis, he can be taught to relax and listen attentively, often with unconscious attention. The patient comes for treatment because of physical or emotionally induced illness. His coming is in itself an implication that he will accept your suggestions or advice in helping him to get well. This includes hypnotic treatment.

There are numerous ways to use hypnosis and numerous conditions in which hypnosis will benefit patient and doctor. It may be used to get better cooperation from the patient; or to help the patient accomplish a

goal that consciously he cannot reach alone. It may be utilized to give the patient ideas that he will thoroughly consider, which consciously he might pass over and discard.

Hypnosis has had wide use in childbirth and as surgical anesthesia. It has helped to relieve bedwetting, thumb sucking, smoking, over-eating and other compulsive acts. It is a great aid in asthma, neurodermatitis and nervous tics and in comforting patients in terminal illnesses, lessening frequency, or even permitting discontinuance of opiates. It may remove phantom pain in amputated limbs and relieve migraine headaches or hysterical neuroses. Hypnosis has been helpful in the management of premenstrual tension, dyspareunia, functional dysmenorrhea, frigidity, impotence and functional uterine bleeding.

I feel that the best use for hypnosis in daily practice is in the realm of patient cooperation, in teaching him to relax for various examinations, notably: pelvic, rectal or even abdominal palpation. Other daily uses may be anesthesia for minor operative procedures or hypodermic injections. Childbirth, control of lactation, and reduction of fears of office visits are other areas where hypnosis can be useful. Major operative procedures may be accomplished in deep trance subjects.

There are doctors who propose that only psychiatrists should use hypnosis. If that be valid, then only psychiatrists should give even simple advice or suggestions to patients as these simple things are in essence forms of hypnosis. Certification in psychiatry is not a requisite to give simple advice to a patient who is normal or only mildly neurotic. The psychiatrist should not have to give hypnotic anesthesia for a laceration or a broken bone when this would be better for the patient than local or general anesthesia nor should a psychiatrist need be present in a delivery situation.

The physician should be psychiatrically oriented or well grounded in psychiatry through formal or personal pursuit and training before he endeavors to treat compulsive behavior and other personality problems many patients use to maintain their psychic equilibrium. Psychosomatic complaints originate in a patient for a specific reason, usually a personality protective device. However, many complaints may linger for years thereafter as a habit even though no longer needed. Simple suggestions in hypnosis can make these patients comfortable quickly and easily. Other psychosomatic complaints continue only because new life situations demand some form of adjustment. I do not propose a non-psychiatrist or non-psychiatrically oriented person to treat these illnesses through hypnosis any more than I would expect non-neurosurgeons to remove brain tumors. I also would not expect to treat surgically a heart malformation without special training. On the other hand, hypnosis can help in many of these illnesses to an extent commensurate with the doctor's ability to understand and deal with people.

Conversion and other psychophysiologic symptoms are utilized by patients to meet maladjusted mental needs as a crutch to help meet environmental demands. This crutch should not be "kicked out from under the patient" by hypnosis without first thoroughly understanding and re-patterning the personality structure responsible for its presence. If the crutch is carelessly removed, equal or even more severe psychologic or psychophysiologic symptoms may appear. In any circumstance the crutch must be discarded by the desire of the patient rather than the insistence of the hypnotist. If the patient is only encouraged to throw away his crutch, he will take his own time and discard it when he is ready. In this way you are allowing the patient to set the pace of his therapy for which he will be grateful.

The patient who has problems requiring extensive psychiatric treatment will manifest these needs by his lack of cooperation, in not staying in a trance or refusing suggestions in a trance. The refusal to cooperate indicates conflicts between the patient's need and motivations and the doctor's suggestions.

Personal experience with hypnosis will demonstrate to every conscientious doctor what he is capable of accomplishing for his patients through this medium. The doctor who tries too much and repeatedly oversteps his competence in the use of hypnosis will

find his patients keeping their symptoms or developing other symptoms of a more debilitating nature.

I am of the opinion that every doctor of medicine can benefit his patients by being thoroughly acquainted with hypnosis and its uses. Of course, reasonable care should be utilized in the selection of patients for hypnosis just as for other forms of therapy. There need be no more mystery connected with hypnosis than there is in any other medical procedure. Many of the medical procedures of today would have been considered mysterious and unusual to the doctor of fifty or even twenty years ago. A modern jet or an automobile would be an extreme anxiety producing item to a person who lived years ago and had not seen their development and use over the years. Only with contact, use, knowledge and understanding does man progress. Attaining knowledge of hypnosis and utilizing it after proper training will abolish the mystery connected with it.

All too often patients visit our office and after history taking and physical examination we can find no organic reason for the symptoms presented. Frequently we seek the use of tranquilizers or phenobarbital because we have no alternative for this nervous patient. With hypnosis as an additional tool in the medical armamentarium we can offer more to these patients than ever before.

Each day we discover more uses for hypnosis. It is very gratifying to help a patient lift the burden of certain illnesses which they have carried for years by teaching them through hypnosis to either control, eliminate or ameliorate their symptoms. Of course, there will be failures as with any other medical treatment. There will be patients who may not go into a hypnotic state with one doctor but will for another.

Hypnosis can be used with ease only with intelligent people. Idiots, morons and severely psychotic patients are difficult to hypnotize. It is the patient's cooperation and motivation that enhances the hypnotic trance development. Any one can produce a hypnotic state in certain individuals, but a medical and personal knowledge of the patient is necessary to suggest in hypnosis the things a patient can accept and incorporate into his own personality structure. The acceptance by the patient of needed suggestions, according to their understanding of these suggestions, is the key to the successful use of hypnosis.

The following case histories illustrate some of the principles above set forth:

Case 1: P.D., age 11, was brought to the office after a fall while roller skating. Physical examination revealed a collies fracture of the right radius and X-rays confirmed the clinical impression. During physical checking of the arm the patient was talked into a deep trance and anesthesia was suggested for the entire arm. The further suggestion was made that this anesthesia would persist until I asked it to leave even though the patient would be awake from now on. She agreed readily to these suggestions. After making X-rays with complete comfort the fracture was broken clear through by reversing the angulation. This, as you know, gives a very audible snap like the breaking of a stick. To this sound the patient asked, "What was that noise?" She, at no time, showed evidence of pain, and though two others in the room questioned her extensively concerning the possibility of pain, she told them there was none as the arm was completely asleep. This patient remained awake the entire time after the induction; her first time to use hypnosis. After casting the arm I asked the child to let the arm go to normal and she followed the post hypnotic instruction immediately.

I have used this procedure for children many times in the past three years for broken arms, fingers and legs. Sometimes, however, I set the arm while the patient is in the trance rather than in a post-trance anesthetic state.

Case 2: Childbirth. This is the account of a delivery in a very nervous gravida II, 24 yrs. The patient had an older baby 3½ years of age.

Examination the day before revealed the cervix to admit one finger. The following day, after an hour's labor at home, the patient timed contractions and came to the office to check on progress. She was then 3 cm. dilated, 80% effaced with cephalic presentation and 1 plus station. She went directly to the hospital where she was again checked, perhaps 30 minutes after the office examination, and was found to be 5 cm. dilated.

After thirty minutes in the hospital and 6-7 cm. dilatation the patient asked for a shot of medicine so she could feel the difference; she being in a trance at this time. I gave her 50 mgs. Demerol and ½ cc. Lorfan intramuscularly. She became nauseated as she had said before that all pain shots made her "sick." In less than 20 minutes from the time of the shot she told me the head was in her vagina. A quick check proved her correct and she

was transferred to the delivery room. She had previously requested gas so she would not know anything about the delivery. So immediately upon the mask being placed on her face, using straight oxygen, she developed perfect anesthesia from waist down as I had trained her to do. And to comply with her request, at time of episiotomy I asked the anesthetist to give five breaths of cyclopropane. This was done without any visible signs of discomfort. A RML episiotomy was done and the baby was spontaneously delivered with the next contraction. The episiotomy was sutured under oxygen only and as with all my patients the last suture placement caused a twitch of the patient. Upon my request she slowly awakened to full consciousness over a 15 minute period. I knew she would then have the feeling her anesthetic had had time to wear off. She was then informed the baby was delivered, and she, as nearly all hypnotic patients, couldn't believe it. She also did not remember the last suture placement. Nurses about the hospital remarked that she must have always been a staunch, calm individual. However, when both she and I told them of her usual nervousness and apprehensions, all were amazed.

I have delivered other mothers who never required any medications and still others who required more than this patient, all using hypnosis. One primipara, posterior, utilized 19 hours of hypnosis and went through the entire delivery without medication. I tell my patients that whether or not we use hypnosis in the delivery, medication will be used if indicated or if they request it.

Case 3: A child, age 7, had been afraid of shots since age 2½ (when forcibly held while being given two hip shots) was induced in 2-3 minutes to a hypnotic level by which she was able, through suggestions and dissociation, to view television in her living room. She also enjoyed eating cookies and drinking milk while viewing her favorite TV program. Still in the office the child was given polio and tetanus hypodermics without any evidence of awareness of the procedure by sound or body movements. While still in hypnosis the child was reoriented to her presence in my office and awakened; after which she did not believe that anyone had given her a "shot." This use of hypnosis for hypodermic injections has been used for hundreds of patients in my office in the last three years. Both children and adults appreciate the comfort offered by this approach to common discomforting procedures.

Case 4: Asthma. A 14 year old boy, who for ten years had incurred medical and hospital bills of $1,000-$2,000 per year, responded well to management by the use of hypnosis. This boy could not ride a bike or participate in any sport. In hypnosis he told of an operation at the age of 4 years in which he experienced choking while under the anesthetic. This experience seems to have initiated his asthmatic history. In the trance this child felt he needed a fear if he was to get over his asthma. I agreed that by all means he would have a fear if he wanted and needed one. I thought since he could not participate in sports in the past due to his asthma that he might like to have a fear of a ball coming straight at him. But further to satisfy, though limit, his desire, I requested he only be afraid of this ball as it came at him if it were purple. He agreed to this readily.

The patient is now 17 years old and is still waiting to see a purple ball coming at him to get really afraid. He has had no asthma except on the anniversary of his operation. This is just for practice so he can have asthma again if he needs it and he doesn't want to be completely out of practice if he needs an attack. He is happy, rides his bike to school, makes much better grades in school, and participates in all sports except football. Each year his anniversary attack, although it lasts for two hours, has been less and less severe. This past year just a few wheezes and some chest tightness occurred on the anniversary, again lasting just two hours.

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Preliminary Report on a Multiple Choice Word-Picture Association Test

KENNETH HARRISON, PH.D.

The present report describes the construction of a projective test capable of discriminating between neurotic and normal children with norms that might be useful for screening in educational and vocational guidance. It is also believed that the test would provide a method for use in clinical work of probing the fields of disturbance among maladjusted children.

Construction of the Test

The Multiple Choice Word-Picture Association Test consists of two parts: (a) a word list (Table I) compiled on the basis of experience and previous experiments with the word association method and classified under the headings of Home and Familial, Social, and Anxiety-prone and (b) a selection of five pictures (in random order) for each word depicting themes of association, which were classified into five categories, Normal Response, Anxiety, Aggression, Depression, and Narcissism-Exhibitionism. The subject was instructed to choose from the pictures that one which came nearest to the thoughts or ideas that came into his head after he heard the word. Failures to react to the stimulus-word or reactions different from the themes of the offered pictures were noted.

For the purpose of this preliminary experiment the test was devised for boys only. Versions suitable for girls and for male and female adults are being devised. The test was administered individually to 60 boys (aged 9-11) attending three primary schools in the city of Belfast, Northern Ireland, and to 60 boys referred to the author in his capacity as educational psychologist and classified as neurotics (n=27), delinquents (n=17), truants (n=11), and others (n=5). The last group were boys with special problems in educational and vocational guidance.

From a comparison of the picture choices of the normal and neurotic groups it was possible to separate them at the 10 per cent level in the cases of seven words and at the 20 per cent level in the cases of four words (Table I). Chi-squares were calculated from tables with two columns (normal and neurotic frequencies) and five rows (categories of picture response, rare cases of choice of "different" themes from those offered or of failure to respond being assigned arbitrarily to the cells with the lowest frequencies). On the basis of these results positive (P) indicators (responses found more frequently in the normal group) and nega-

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TABLE I

Words with Responses Differentiating the Normals and Neurotics

Word	Chi-Square	P	PICTURE RESPONSES: Postitive (P) Indicators	PICTURE RESPONSES: Negative (N) Indicators
2. Street	8.591	<.10>.05	E Narc.	A Aggr.; D Depr.
5. Body	6.074	<.20>.10	A Narc.	B Aggr.; D Depr.
7. Arm	10.694	<.05>.02	D Aggr.	C Narc.; E Depr.
8. Pictures	15.245	<.01	C Norm.	A Depr.; B Aggr.; E Anx.
9. Dirt	14.960	<.01	D Aggr.	A Anx.; C "Norm."; E Depr.
12. Brother	7.344	<.20>.10	C Norm.	B Depr.; D Aggr.; E Anx.
13. Knife	8.447	<.10>.05	B Norm.	A Anx.; D Depr.
14. Water	10.554	<.05>.02	A Norm.	B Anx.; D Aggr.
16. Sister	16.333	<.01	E Norm.	A Depr.; B Anx.
19. Father	7.335	<.20>.10	E Norm.	C Narc.; D Anx.
20. Gun	6.363	<.20>.10	C Narc.	E Depr.

Narc.—Narcissism
Norm.—Normal
Aggr.—Aggression
Depr.—Depression
Anx.—Anxiety

TABLE II

P-N Scores of the Various Groups on the Provisional Adjustment Scale

Adjustment Scale P-N Score	Normals F	Normals Cumul. Percent.	Neurotics F	Neurotics Cumul. Percent.	Delinquents F	Delinquents Cumul. Percent.	Truants F	Truants Cumul. Percent.	Others F	Others Cumul. Percent.	All Clinicals F	All Clinicals Cumul. Percent.
8 to 9	4	100										
6 to 7	8	93			1	100					1	100
4 to 5	15	80			2	93					2	98
2 to 3	15	55	1	100	4	82					5	95
0 to 1	10	30	4	96	4	59	3	100	2	100	13	87
—1 to —2	6	13	4	82	4	35	3	73	2	60	13	65
—3 to —4	2	3	9	67	2	12	4	45	1	20	16	43
—5 to —6			5	33			1	9			6	17
—7 to —8			4	15							4	7
N	60		27		17		11		5		60	
Mean	+3.00		—3.35		+1.06		—2.05		—1.10		—1.73	
S.D.*	2.903		2.658		2.709		1.831				3.025	

*Sheppard's correction has been employed in the calculation of the S.D.'s owing to the narrowness of grouping.

tive (N) indicators (responses found more frequently in the neurotic group) were developed (Table I). A subject's P-N score was considered to represent his relative standing on the provisional Adjustment Scale. P-N scores were calculated for the 60 normals and for the 60 clinical cases.

Results

On P-N scores the normals were differentiated significantly from all groups; from the neurotics (C.R. 9.92), from the delinquents (C.R. 2.51), from the truants (C.R. 7.33), and from the clinical group as a whole (C.R. 8.77). The neurotics were differentiated significantly from the delinquents (C.R. 5.16), but not from the truants (C.R. 1.67). The results suggest that in general the delinquents were less maladjusted than the other clinical groups although there is apparent much variability in this group.

With a tentative cutting point at 0 on the provisional Adjustment Scale 82 per cent of the neurotics, 73 per cent of the truants, 65 per cent of all clinical cases (improved to 77 per cent by the omission of the delinquents) and 13 per cent of the normals would be screened off.

Summary

A devised projective test (the Multiple Choice Word-Picture Association Test) was administered individually to 60 normal boys and to 60 boys referred for psychological help.

The normal and neurotic groups were discriminated significantly on a number of responses. Indicators of adjustment (P) and maladjustment (N) were established, and all cases were assigned P-N scores on a provisional Adjustment Scale.

Acknowledgments: I wish to thank the following people for their cooperation and help: Dr. Demay, Superintendent, and Dr. P. O'Reilly, Coordinator of Research, Saskatchewan Hospital, North Battleford.

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Acute Myocardial Infarction and Electroconvulsive Therapy

J. THOMAS UNGERLEIDER, M.D.

Acute myocardial infarction remains one of the few contraindications to electroshock treatment. Patients with healed myocardial infarction have received electroshock without adverse effects.[1,2] There is brief mention in the literature of one suicidal patient with an acute myocardial infarction who survived electroshock. This patient had one treatment three days after his infarct and recovered without difficulty.[3,4] The purpose of this paper is to present the effect, both clinical and electrocardiographic, of electroshock on a patient with an acute myocardial infarction. This does not, however, imply that acute infarction should no longer be considered a contraindication to electroshock. Fluoroscopy of the heart during the tonic phase of the electrically induced convulsion reveals asystole, while the clonic phase is often accompanied by tachycardia, atrial fibrillation, and arrhythmia.[5]

Coronary Deaths and Electroconvulsive Treatment

Fatalities occurring after electroshock are not uncommonly due to coronary artery disease. Of the 67 deaths from "convulsion treatment" which occurred from 1947 to 1952 in England and Wales, ten were due to "coronary occlusion and atheroma."[6] Of the 33 deaths following electroshock in the American and English literature prior to 1949, two were due to "coronary occlusion and myocardial infarction."[7] One of these patients died 90 minutes after his 12th electroshock treatment, having complained of angina just after recovering from this seizure. Autopsy revealed a thrombosis of the descending branch of the left coronary artery with "very early myocardial infarction."[8] The other patient died 12 minutes after his eighth electroshock treatment. Autopsy revealed an extensive obliterating coronary artery sclerosis with a two to three week old left ventricular myocardial infarction.[9]

Another fatality due to electroshock treatment of a patient with an acute myocardial infarction was reported in 1950.[10] Death occurred just after the sixth electroshock treatment and autopsy revealed a two week old septal and right ventricular infarct. All six treatments had been given in the 12 day period prior to death. Rupture of an acute infarct following electroshock treatment has also been reported.[11] The patient died one half hour after the 21st treatment and a four to six day old ruptured myocardial infarction was found at autopsy.

Within a few hours after a coronary occlusion, there are no demonstrable changes in the myocardium. From three to six hours after the infarct, beginning focal hyperemia is seen. From four to ten hours one finds slight loss of striation, hemorrhage, infiltration of leukocytes, changes in nuclei, and interstitial edema. After two to fifteen days the picture usually associated with a myocardial infarction is seen.[12]

Coronary thrombosis without myocardial infarction has also been responsible for electroshock fatalities.[10,13]

The Electrocardiogram and Electroshock

Electrocardiographic changes frequently occur following the induced convulsion, both in normals and in patients with cardiovascular disease. In one electrocardiographic study of 42 psychotic patients, 34 had increased T wave amplitude following electroshock treatment.[14] Thirty-seven of these patients had no cardiovascular disease and there were no differences in the records of the five who did. There were no S-T changes recorded. In another study, the increase in T wave amplitude, which occurred especially in leads I and II, returned to normal within five minutes.[3]

A case of T wave inversion in leads I and II following electroshock therapy has been

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reported.[15] This patient had no known cardiovascular disease and had a minor seizure immediately following electroshock treatment. One hour post-treatment, she developed a series of major seizures which were abolished only with ether anesthesia and intravenous sodium barbital. The T wave changes were not present one hour after these seizures ceased but were first observed two days thereafter and then persisted for six weeks.

In a series of 50 patients without cardiovascular disease, pre-shock and post-shock electrocardiograms were taken in conjunction with 65 major and 35 minor seizures. In seven instances the T waves were flattened, in six the T waves increased in amplitude, in three there was S-T segment depression, and an instance of T wave inversion occurred.[15] The first three types of electrocardiographic abnormalities disappeared within seven to fifteen minutes after the onset of the convulsive seizure.

Various electrocardiographic arrhythmias also occur following electroshock treatment, especially in patients with old coronary artery disease. These, however, disappeared in one study, within a day following the treatment.[1] While the nature of these arrhythmias does not concern us here, it is felt that their most important cause is the strong surge of vagal tone which follows the electric stimulation and which appears to have its most intense expression at about the same time the convulsion subsides.[16] There is no apparent relationship between the amount of current, the duration of seizure and the severity of the electrocardiographic changes. Kalinowsky concludes that the electrocardiographic changes are negligible in electroshock treatment.[5]

Case Report

The patient, a 68 year old white woman, was hospitalized for 69 days in August of 1952 with a one week history of unusual behavior. The patient was well until several months prior to admission at which time she began to express the belief that she was being mistreated by her daughter, her landlord, and her neighbors. One week prior to admission, the patient spoke of her apartment being "wired for sound." She began to hear accusatory voices and, on the day of admission, believed she saw a neighbor coming at her with a knife. The patient then attempted unsuccessfully to jump out of her third story apartment window in order to escape from this woman.

The patient had been hospitalized for the first time at University Hospitals in 1940 because of a skin disorder which was partly attributed to psychogenic factors. Her cardiovascular status in 1940 revealed only a moderately accentuated aortic second sound and a very soft systolic murmur in the aortic area. Her second University Hospitals admission was in February of 1941 for removal of nasal polyps. No cardiovascular abnormalities were recorded at that time. The patient was again hospitalized in 1945, at another local hospital for nasal operations of undetermined nature. She had been followed in the allergy clinic for about two years prior to the present admission because of recurrent asthmatic attacks of five to seven years duration. These were relieved by aminophylline, ephedrine and phenobarbital.

The pertinent findings on the admission mental status examination were as follows: The patient was quiet, clean and neatly dressed. She appeared calm while relating the delusional material and frightening hallucinations mentioned above. During the examination she spoke in an unconcerned manner of the voices which were calling her a "God damn woman" and of the people who were about to kill her. Her controlled manner was in marked contrast to her behavior just prior to hospitalization when she tried to escape her imaginary pursuers through an upper story window. She was well oriented in all spheres with a good fund of general information. Judgment and insight were obviously lacking.

The physical examination on admission revealed an obese, well-developed white woman in no pain or acute distress. Bp 135/80. R 20. P 88. T 37. Positive physical findings included occasional asthmatic musical rales with an increased expiratory phase diffusely over both lungs. The left border of cardiac dullness was 10 cm. to the left of the midsternal line in the fifth inter-space. One + pitting edema was present involving the lower extremities bilaterally. Regular sinus rhythm was present with no murmurs nor abnormalities of the pulses.

Admission laboratory work revealed normal urinalysis and hemogram. Serum cholesterol was 308 mgm. per cent and serum bromides were negative. Chest films revealed pulmonary emphysema with prominence and tortuosity of the aorta plus right mid-lung fibrosis. Skull films were negative. X-rays of the spine revealed advanced senile bony changes.

During the two-week period following admission, the patient presented a changing picture with the appearance of varying degrees of impairment of orientation. The persecutory delusions and hallucinations were of changing intensity during this period and at times depressive trends were present. Some features of organic as well as functional impairment were thus suggested. It was decided to administer a course of electroshock treatment. Prior to the initial treatment, an electrocardiogram was taken and interpreted as "probably within normal

limits although the Q-T interval is prolonged" (Figure 1). The patient's first electroshock treatment was on the 16th hospital day. She then received five additional treatments during the following 12 days (hospital days 16-28). All treatments were given under sodium thiopental anesthesia with succinyldicholine or gallamine triethiodide (Flaxedil) in sufficient amounts to markedly attenuate her convulsion. Throughout the procedure oxygen was administered under positive pressure with bag and mask until spontaneous respirations returned.

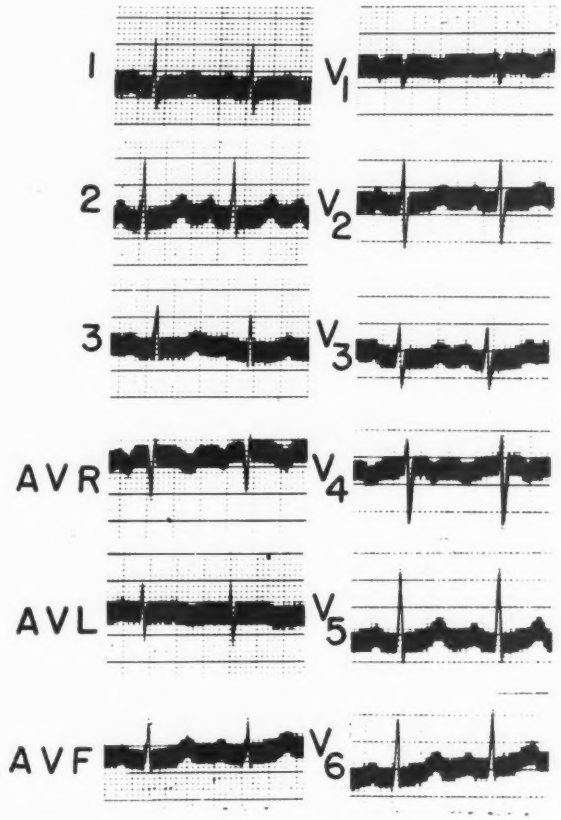

Figure 1. Admission electrocardiogram, prior to electroshock treatment. Interpreted as probably within normal limits although the Q-T interval is prolonged.

After the fifth electroshock treatment on the 26th hospital day, it was decided to include the patient in a study then under way of the electrocardiographic effects due to electroshock treatment. She was by this time calmer, happier, and easier to manage. Hallucinations were less frequent. The patient was then, as throughout her entire hospital stay, asymptomatic with respect to her cardiovascular system. Thus, an electrocardiogram was taken just prior to the patient's sixth electroshock treatment on hospital day number 28 (Figure 2), as well as immediately following the induced convulsion (Figure 3), but these were not interpreted until later that afternoon. At this time it was noted that the pre-shock record revealed evidence of antero-septal myocardial infarction. Another record was taken several hours following the shock treatment, and this showed the previously mentioned changes to be persistent (Figure 4A). The electroshock treatments were discontinued. During the next two weeks, T wave changes occurred which were consistent with the evolution of the infarct (Figure 4B and C). The corrected sedimentation rate on the day following the electroshock treatment was 19 and dropped to 9, ten days later.

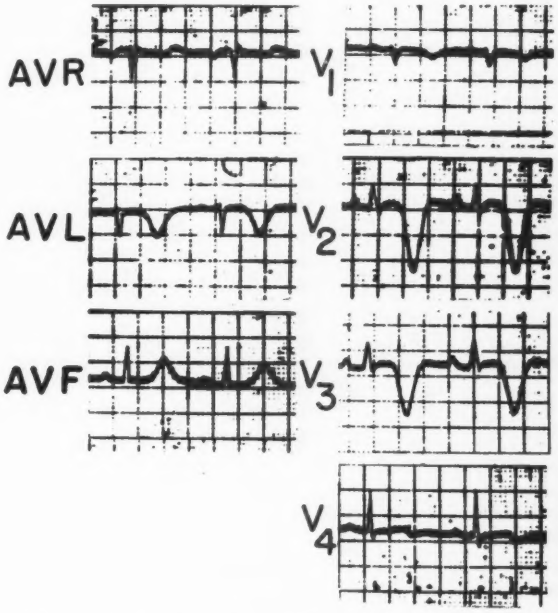

Figure 2. Immediately prior to sixth electroshock treatment (16th hospital day). Interpretation: In comparison with Figure 1, AvL shows a very small R wave and the T wave is deeply and symmetrically inverted. In AvF the T wave is tall and symmetrically peaked. In V_1 the T wave is more deeply inverted and in V_2 and V_3 it is sharply and symmetrically inverted. There is terminal inversion of the T wave in V_4.

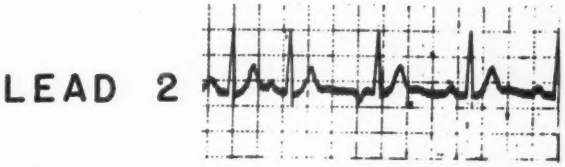

Figure 3. Immediately following the sixth electroshock treatment: Lead 2. Lead 2 shows depression of the S-T segment and atrial premature beats.

The patient became more severely disturbed following the discontinuation of the electroshock treatments, refused to eat, was very agitated and unable to sleep. Because of this, she was given one further electroshock treatment on the 58th hospital day. A pre-shock electrocardiogram (Figure 5A) then revealed return towards normal. However, a post-shock record revealed more deeply inverted T waves in the antero-septal area (Figure 5B). Treatments were again discontinued and an electrocardiogram five days after this final electroshock treatment (Figure 5C) revealed the residual

T waves in AvL and V_2 similar to the pre-shock record of the 58th hospital day (Figure 5A).

The patient was transferred to another hospital on her 69th hospital day. Discharge diagnoses were: "Chronic brain syndrome associated with cerebral arteriosclerosis with psychotic reaction"; and "myocardial infarction due to arteriosclerotic coronary thrombosis." The patient expired five months following transfer to the other hospital. No electrocardiogram was done at this hospital and the

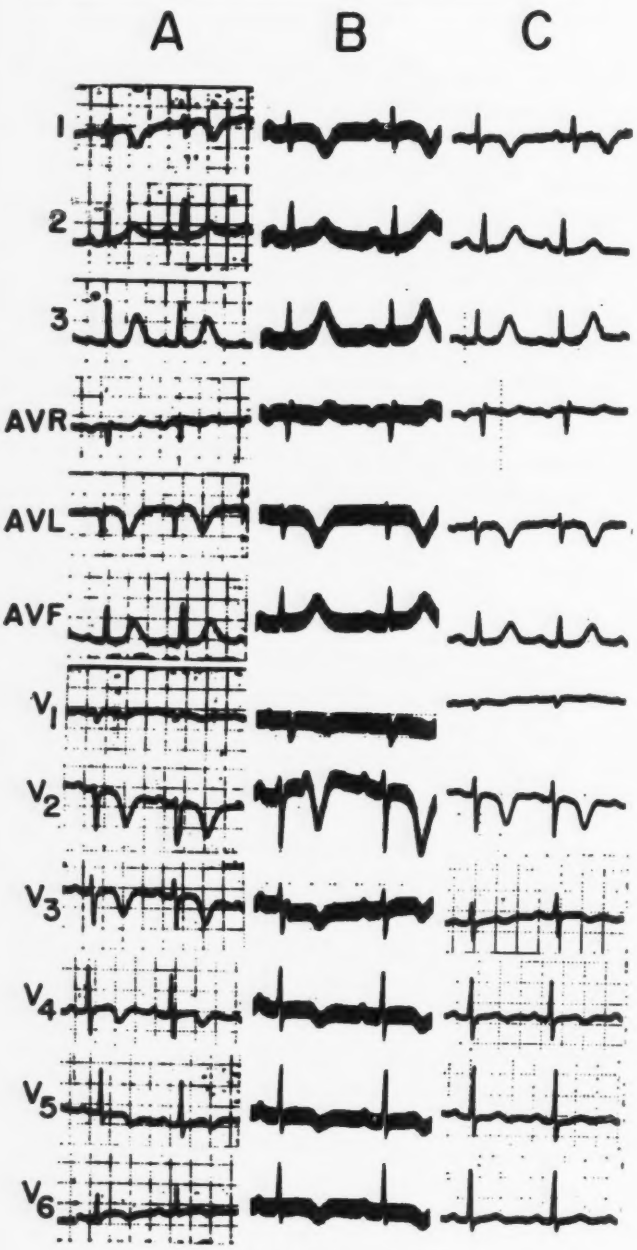

Figure 4.

A—Several hours following the sixth electroshock treatment. The record is essentially the same as the pre-shock tracing (Figure 2) and shows persistence of these changes.

B—Five days after the sixth electroshock treatment (21st hospital day). There are waning T wave changes consistent with the evolution of a recent antero-septal infarct.

C—Two weeks after sixth electroshock treatment (30th hospital day). Further improvement in T waves has occurred, particularly over the lateral precordium.

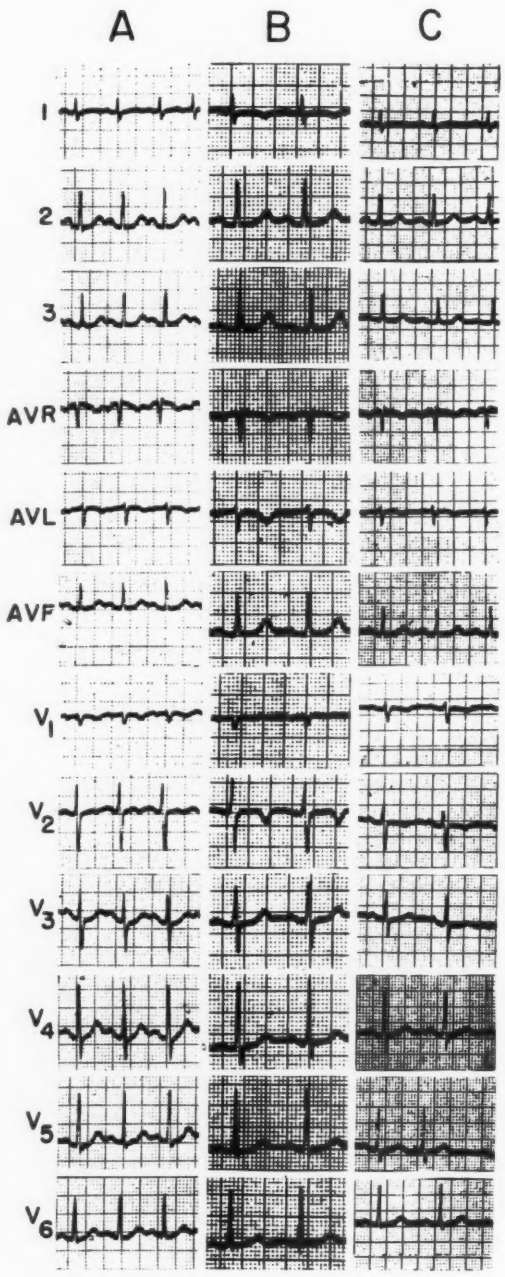

Figure 5.

A—Immediately prior to the seventh electroshock treatment (58th hospital day). This record shows a low T wave in Lead I and inversion of the T wave in AvL and V_2.

B—Immediately following the seventh electroshock treatment. The T wave is inverted in Lead I and more deeply inverted in AvL. V_2 now reveals a sharp inverted T wave.

C—Five days after the seventh electroshock treatment (63rd hospital day). This record shows a low T wave in Lead I, an inverted T wave in AvL and a slightly inverted T wave in V_2.

patient received no electroshock treatments. The patient terminally was dyspneic though this was relieved by sitting up. Pulse was 120 and irregular and diffuse dry squeaking rales and rhonchi were heard over the lungs. A diastolic murmur was described over the mitral valve. Expiration was attributed to coronary thrombosis and acute cardiac decompensation. No autopsy was performed.

Discussion

This patient received at least one electroshock treatment at a time when her electrocardiogram showed the changes of an acute anteroseptal myocardial infarction. There was no accentuation of electrocardiographic abnormality following the electroshock treatment. (It was not yet known that the patient had an infarct at the time of this treatment.) Likewise, the patient manifested no symptoms of coronary artery disease at any time during her hospital stay though this is not uncommon in psychotic mental patients.[17]

After the patient's electrocardiogram had returned nearly to normal, her clinical condition made a further electroshock treatment necessary. Although she seemed to withstand the procedure without difficulty, her electrocardiogram after this treatment showed T wave changes suggestive of recurrent insult to the antero-septal myocardial area. It is uncertain if the patient's demise was hastened by or related to this episode of myocardial infarction occurring during the period of electroshock.

Summary

A case history has been presented of a 68 year old woman who inadvertently received an electroconvulsive treatment for a psychosis during an acute myocardial infarction, which was documented electrocardiographically. She apparently sustained the procedure without ill effect.

Acknowledgment: I would like to express my appreciation to Dr. Harold Feil for interpretations of the electrocardiograms in this study.

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Use of Trifluoperazine in Chronic Psychotic Patients

HEINZ J. EXT, M.D.

In October 1958, we began using a new phenothiazine derivative, trifluoperazine, in chronically ill, refractory patients. Early reports of its ability to relieve psychotic manifestations and restore initiative in apathetic schizophrenics prompted our use. For instance, in England, Madgwick et al. observed an "awakening of interest, a desire to take part in occupations and recreations of various kinds" in chronic schizophrenic patients given trifluoperazine.[1] Their findings seemed to parallel those of Rudy and co-workers in the United States, who reported a marked transformation of personality in chronic patients on trifluoperazine and of their subsequent adaptation to the hospital social milieu.[2] Our initial experience with the drug in a few patients proved promising and indicated that further trials were warranted.

Patient Selection

To evaluate further the drug we selected 60 chronically ill men who had been hospitalized an average of 11.2 years. Table I shows the composition of this series. Fifty-five were schizophrenics, three were psychotics with mental deficiency, one was psychotic due to trauma, and one was psychotic due to alcohol. The symptom complex seen in the majority of patients consisted of hallucinations, ideas of reference, delusions, hostility, combativeness, and compulsivity and mannerisms. Catatonic stupor and posturing, destructiveness, and homicidal tendencies were displayed by a few patients. These symptoms had remained essentially unaltered by somatic therapies.

Dosage

Most of the patients were started on one 5 mg. tablet of trifluoperazine, b.i.d. A few were started on 2 mg., b.i.d. Dosage was increased every three to four days by increments of 2 to 5 mg. It became evident after the first ten or so patients were treated that gradually increasing dosage lessened the incidence and degree of side effects, particularly extrapyramidal symptoms. A daily dosage of 25 to 35 mg. proved sufficient to produce an optimum effect in the majority of our patients. The highest dose given was 60 mg. a day. During the study, patients were treated from four to 40 weeks. Patients who could leave the hospital were continued on maintenance therapy at the dosage which proved effective. Throughout the study we continued to make efforts to get patients to participate in group therapy.

Patient Response

Table II summarizes overall patient response during the 40 weeks of using trifluoperazine and shows that 46.6% of the patients improved significantly. The significantly improved patients were those who began to take effective part in group activities, including such occupational therapy as grounds work, farming, work in the hospital cannery, mattress shop, shoe shop, and other jobs which operate in much the same way as their non-institutional counterparts. Having them take part in these activities was the first major goal in their rehabilitation. Of those showing significant improvement, seven were later placed on convalescent status and five had successful home visits.

TABLE I

Composition of Study Group and Results of Trifluoperazine Therapy

				Significantly Improved	
Schizophrenic Reaction:	No. of Pts.	Average Age (yrs.)	Aver. Duration of Illness (yrs.)	No. of Pts.	% of Pts.
Paranoid Type	22	49.5	8	13	54.5
Catatonic Type	14	43	16	5	35.7
Hebephrenic Type	8	44	25	4	50
Simple Type	6	44	11	1	16.7
Mixed Type	4	30	7	1	25
Childhood Type	1	18	3	0	0
Psychosis with Mental Deficiency	3	47	12	2	66.7
Psychosis Due to Trauma	1	42	15	1	100
Psychosis Due to Alcohol	1	56	6	1	100
Total Group	60	41.5	11.2	28	46.6

From Middletown State Hospital, Middletown, New York.

TABLE II

Effect of Dosage and Duration of Treatment on Efficacy of Trifluoperazine Therapy in Chronic Psychotics

Max. Dosage (mg./day)	No. of Pts.	Average days for Favorable Response*	Average days of Treatment†	% Improved	% Significantly Improved
14 - 17	3	17	35	100	33
20	8	37	79	75	62
25 - 27	9	58	106	86	33
30 - 32	27	47	103	74	48
35	6	19	30	83	50
40	6	28	47	67	50
60	1	—	104	0	0
Total Group	60	34.3	72	74.6	46.6

*Patients who did not show improvement are not included in the averages. Improvement was noted as soon as the effective dosage level was reached.

†Duration of treatment listed is limited to the period of study; most patients were continued on trifluoperazine after the study. Effective results were continued, with either maintained or increased effectiveness in group thrapy. No patients relapsed, and four previously unaffected patients showed improvement witr continuing therapy after the close of the study.

TABLE III

Relation of Trifluoperazine Dosage to Occurrence of Extrapyramidal Symptoms

Patient	Age	Dosage (mg./day) at Occurrence of Symptoms
J.M.	58	14
J.W.	34	15*
P.S.	60	15*
S.H.	27	15
S.U.	41	15
B.E.	63	17
S.I.	32	17
M.I.	67	20
M.U.	51	22
S.T.	51	22
F.K.	25	25
B.A.	42	25
L.I.	48	25
L.O.	49	27
E.A.	46	30
R.S.	57	30
J.C.	56	30
C.S.	56	30
G.L.	35	30
S.E.	37	30
W.A.	55	30
D.E.	39	30
J.O.	57	30
P.R.	42	32

*Treatment had to be discontinued.

Twenty-eight percent of the patients were rated as showing slight improvement. That meant they became more cooperative in hospital routines. Few, however, showed any initiative, in contrast to those who were rated significantly improved. For example, one catatonic patient, when given trifluoperazine, became less seclusive and withdrawn, and now sits on a chair in the sunlight of the ward instead of lying huddled in dark corners. Whether he will participate in hospital activities in time remains to be seen. It is noteworthy that his apparent personality deterioration seems checked, that he is closer to a stage where simple occupational and other therapies may be employed to possible advantage. (This patient has made great progress since the close of the study. He now participates in all hospital activities and joined a play-reading group where his performance is outstanding. He has progressed to such an extent that placement on convalescent status and release from institutional care now can be taken into consideration.)

A breakdown by diagnosis, age, years of illness of patients rated significantly improved is given in Table I. Paranoid and hebephrenic types responded best; in them hallucinations and delusions usually subsided rapidly or no longer were bothersome. Marked improvement soon followed. An example of a paranoid type schizophrenic patient who showed significant improvement is given in the following case history.

L.R., age 25, was hostile and aggressive and spent much time in restraints or under special care. During six years hospitalization, he had been treated with electric shock, prochlorperazine and various other therapies without improvement. Trifluoperazine was instituted and dosage was raised gradually to 30 mg. Over a period of 30 days, he showed no improvement. When the dosage was increased to 40 mg. daily, he no longer had hallucinations and became less aggressive and hostile. On 40 mg. of trifluoperazine daily he continued to improve in his relationships with other patients and hospital personnel, gradually became less delusional, and after another 30-day period was able to go home on a month's leave.

Improvement of catatonic patients was less spectacular, which is generally true with other tranquilizing agents we have used. It is worth noting, though, that 35.7% showed significant improvement. This rate of response, although low compared to the response in paranoid patients, is better than

we have observed to date with phenothiazine derivatives. For the first time since their hospitalization, patients given trifluoperazine were willing to perform minor housekeeping chores and showed more interest in ward activities.

In general, the pattern of trifluoperazine action is similar to that of other phenothiazines. Target symptoms which were relieved by trifluoperazine therapy were hostility (73% of 22 patients), combativeness (66% of 18 patients), hallucinations (50% of 46 patients), fixed delusions (40% of 32 patients), compulsivity and mannerisms (48% of 17 patients), and ideas of reference (30% of 20 patients). Classic catatonic stupor and posturing, severe destructiveness, and homicidal tendencies were markedly reduced or eliminated.

There seemed to be a sequence of symptomatic relief in patients who were helped during this study. At first, their tension—which had resulted progressively in irritability, hostility, aggressiveness, and violence—diminished, within 10-14 days, and they became interested in activities going on around them. Improved relationships with other patients and staff members generally followed in three to five weeks. Hallucinations subsided and, finally, delusions diminished or disappeared. By this time, however, patients were involved in group therapy activities, so this diminution cannot be ascribed wholly to drug effect.

Side Effects, Toxicity

Varying degrees of parkinsonism and akathisia were seen in 40% of the patients. All but two patients were relieved either by giving anti-parkinsonian agents, or if this was inadequate, by giving anti-parkinsonian agents while temporarily reducing the dosage of trifluoperazine. These two had to discontinue the drug. One recovered gradually from a severe hyperextension of the neck; the other, because of severe anorexia and weight loss due to inability to swallow, had to be transferred temporarily to the infirmary.

Extrapyramidal symptoms seemed to depend as much on individual susceptibility as on dosage or duration of therapy, although no extrapyramidal symptoms developed at doses lower than 14 mg. a day. It appeared that the incidence of extrapyramidal symptoms could be kept low if increases in dosage were spaced three to four days apart. It also proved to be important that the dosage be individualized: Some responded to low dosages, others needed high dosages; some tolerated low dosages (15 mg./day) poorly, others were comfortable on high dosages. In general, the dosage producing improvement in chronic psychotic patients seemed to be near the dosage producing side effects.

As the study progressed, a sequence in the development of side effects was noted. The affected patients first experienced drooling, then difficulty in swallowing and impaired walking, and finally a Parkinson-like tension of neck muscles. As this sequence became apparent, anti-Parkinson agents (Cogentin 2 mg. or Artane 3 mg. once or twice daily) were given at the first sign of side effects. These agents usually controlled the effects without reducing therapeutic gains. For some patients, however, it was necessary to lower trifluoperazine dosage temporarily as well as administer Cogentin or Artane. Table III lists the dosages at which various patients displayed extrapyramidal symptoms. Forty patients were followed routinely with laboratory studies. We saw no signs of liver dysfunction or blood dyscrasias; no convulsions, hypotension or tachycardia occurred.

Discussion

Trifluoperazine proved to be a potent chemotherapeutic agent, producing benefits in chronic patients who had shown meager therapeutic gains from various somatic treatments during their many years of hospitalization. As with other tranquilizing agents, trifluoperazine seemed to affect behavior more than the underlying psychosis. In providing symptomatic relief, it did not, however, tranquilize the patients out of normal activity. Some patients commented that the drug made them "feel more like doing things." In addition, it made matters easier for hospital personnel; for example, idle patients began helping to make beds and perform other housekeeping duties. Paradoxically, or seemingly so, hyperactive patients benefited too. Without loss of drive, they began to channel their energies into accept-

able activities. These gains, in some patients, later led to participation in, and eventful benefit from, occupational therapy. Much of the credit for patient improvement must, of course, go to the staff and an active program of group and other therapies. No special considerations were given to patients receiving trifluoperazine, however, and they had not responded to other pharmacotherapies or to ECT or insulin shock. The drug seemed to be instrumental in starting a reversal of patients' static conditions of thought and action and in that respect may be more than another addition to a growing list of antipsychotic agents. It served to modify patients' actions, or to activate lethargic, withdrawn patients so that their activity could be meaningfully directed. But without an active program of occupational and other therapies, conducted by spirited hospital personnel, much of the good produced by the drug in chronic patients is soon lost. In our experience the drug, to use a loose analogy, is something like a starter on a car. It will turn the engine over (alter static behavior) but after that, proper fuel and maintenance (interaction in reasonably normal situations) are needed to keep the vehicle going.

Summary

Sixty chronically ill psychotic patients, averaging 11.2 years hospitalization and refractory to other therapies, were given trifluoperazine. Dosages given ranged from 2-5 mg. b.i.d. at the start to as high as 60 mg. per day in one patient; 25-35 mg. daily proved optimum for most patients. Duration of therapy ranged from 4 to 40 weeks. Forty-six percent of the patients showed significant improvement. Symptoms relieved by trifluoperazine included hostility, combativeness, hallucinations, fixed delusions, compulsivity and mannerisms, and ideas of reference. Best results were seen in paranoid and hebephrenic patients; catatonic patients also were improved. Trifluoperazine seemed to activate apathetic and lethargic patients and calm hyperactive aggressive or compulsive patients, making it possible to bring both types into beneficial participation in active occupational and group therapies. A high incidence of extrapyramidal symptoms was noted (40%) at dosages of from 14 to 30 mg. daily. Side effects were controlled by anti-parkinsonian agents and/or lowering trifluoperazine dosage in all but two patients who had to discontinue the drug.

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Studies of Anxiety in Schizophrenia

STANLEY LESSE, M.D.

During the past five years we have been studying the relationship between anxiety and clinical symptomology in schizophrenic patients using the following techniques.

1) The use of psychoanalytically-oriented psychotherapy in combination with various tranquilizing drugs (100 patients).

2) The use of parenteral (intravenous or intramuscular) phenathiazine preparations in acutely ill schizophrenic patients (35 patients) or as a means to ameliorate the effects of mescaline or lysergic acid (25 patients).

3) Observations during craniotomy (43 patients) and during and immediately following lobotomy performed under local anesthesia (34 patients).

In all phases of our study, anxiety was defined in the broadest aspect, namely, that it was a psychophysiological phenomenon synonymous with fear, whether the fear was generated by unconscious conflict or actual environmental difficulties. For careful clinical evaluation we divided anxiety into four component symptoms and signs, motor, affectual, vergal and autonomic, which we attempted to quantitate on a four point scale.

I. Mounting Anxiety and Symptom Formation

From our evaluations of detailed histories of patients treated with combined ataraxic-psychoanalytically oriented therapy, from the direct observations of patients under severe, acute stress produced by lysergic acid or mescaline and from observing patients under the acute stress of a craniotomy performed under local anesthesia we found that a direct relationship appeared to exist between the quantitative degree of anxiety and the presence of clinical psychiatric symptoms and signs. It appeared that these symptoms and signs were unconsciously produced secondary defense mechanisms against the pain of the anxiety with the psychophysiological pattern being as follows.

Initially a state of mounting anxiety was produced by an environmental stress (i.e. an internal biophysical stress or an external biosocial problem) with which the patient couldn't cope. This in turn stimulated unconscious conflicts, originating from past traumas, the combination precipitating a pan-anxiety state. It was then that psychiatric symptoms such as hypochondriacal complaints, phobias, obsessive-compulsive states, psychosomatic problems, paranoid states, etc., appeared individually or in a succession, the exact symptoms and pattern of appearance being unique to each patient. As the anxiety mounted, more and more of these defense mechanisms were brought into play. If these secondary defense mechanisms did not quantitatively decrease the level of the anxiety, the patient's ego defenses were overwhelmed and impairment of reality contact ensued with the patient experiencing feelings of dissociation or dissolution or other bizarre aberrations.

This pattern of symptom development could be most dramatically seen when patients with catatonic patterns were given mescaline intravenously. By administering intravenous promazine or chlorpromazine one could, in many instances, ameliorate the anxiety to the extent that many of the symptoms that would have otherwise appeared were not manifested.

We also investigated the problem as to whether individual patients tend to have the same sequence of symptom appearance in response to repeated bouts of extreme anxiety developing secondary to severe stress. Of 50 patients who were observed for one year or more and who had a history of two or more psychotic bouts, 41 (82%) had essentially the same sequence of symptom appearance as the level of anxiety mounted on repeated occasions. Of the 43 schizophrenic patients 38 observed while frontal craniotomies were being performed under local anesthesia, had two or more periods where there was a sharp rise and fall in the anxiety re-

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Presented before the Second International Congress of Psychiatry, Zurich, Switzerland.

action to the stress of the operation. Of the 38 patients 33 (87%) showed essentially the same sequence of symptom appearance with each bout of anxiety. The number of symptoms called into play and the appearance of distortions in the patients' contact with reality seemed to depend upon the quantitative degree of anxiety on each occasion.

II. Anxiety Amelioration and the Disappearance of Symptoms

We observed that the degree of anxiety must be decreased quantitatively *before* a symptom or succession of symptoms disappeared. Among patients treated with the combined tranquilizer-psychoanalytically oriented psychotherapy technique it was commonly observed that symptoms might remain for a period of days after the anxiety was diminished, but there was less emotional impact associated with symptoms. It seemed that a symptom did not disappear completely until the degree of anxiety decreased below a certain threshold which was unique for a given patient.

We also found that the various components of anxiety were not ameliorated simultaneously. This was demonstrated most dramatically during and immediately following the 34 pre-frontal lobotomies performed under local anesthesia. For descriptive reasons we had divided each frontal lobe into two halves, a medial and a lateral half, making four quadrants that had to be cut. Of the 34 patients 29 demonstrated a definite decrease in anxiety during or just minutes following lobotomy. All 29 presented a definite lessening of the motor component, while in 25 the affectual component was ameliorated and in 20 the verbal content was changed. Table I shows that a larger leukotomy was necessary to decrease the affectual component than was necessary to decrease the motor component, while an even greater cut was needed to alter the verbal content. We found that the clinical psychiatric symptoms (i.e. phobias, hypochondriacal reaction, etc.) did not begin to fade until the affectual component of anxiety was first significantly ameliorated.

We performed leukotomies on six patients while they were actively hallucinating. The hallucinations improved or disappeared in five. It was clearly discernible that the improvement occurred secondary to marked decrease in anxiety. For example, two patients had very primitive structuring of their hallucinations which were present in all sensory spheres. When the anxiety was greatly reduced, the tactile and olfactory aspects disappeared and the manifest content of the auditory and visual hallucinations was better organized. In two others the hallucinations disappeared completely before the lobotomy was completed.

TABLE I

Decrease in Components of Anxiety in Relation to Fractional Pre-Frontal Lobotomy

	Component of Anxiety	Number of Cases
Quadrant No. 1	Motor	16
	Affectual	2
	Verbal	0
Quadrant No. 2	Motor	11
	Affectual	11
	Verbal	1
Quadrant No. 3	Motor	0
	Affectual	11
	Verbal	8
Quadrant No. 4	Motor	2
	Affectual	1
	Verbal	11

Dreams behave in a similar fashion. During our treatment of schizophrenic patients with analytically oriented psychotherapy in combination with chlorpromazine or promazine chloride we noted that the affectual impact of the dream was effected first. This was most clearly seen with nightmares and rage dreams. In the early phase of the drug therapy the patients continued to have the same dreams that were accompanied by marked terror or rage prior to the onset of treatment but now the emotional impact was blunted. The manifest content was the same but the dreams were denuded of terror or rage. After a period of a few days the manifest content of the dreams changed too. It appeared that it was not until the level of anxiety was decreased below a certain threshold, which was unique for a given patient, that the content of the dream was changed.

Conclusions

We believe that the results demonstrated by means of these various techniques indi-

cate a direct relationship between the quantitative degree of anxiety and the production of clinical psychiatric symptoms and signs. The findings also point up the fact that the quantitative degree of anxiety must first be decompressed before there can be an amelioration of the various clinical symptoms and signs. It also appears that as anxiety repeatedly mounts in response to repeated stress phenomena, the pattern of symptom appearance tends to be more or less stereotyped in a given patient. These experiments emphasize the fact that the pattern of symptom formation is similar under different types and degrees of stress.

Summary

1. The relationship between anxiety and other clinical psychiatric symptoms in schizophrenic patients was studied using various techniques including combined tranquilizer-psychotherapy, hallucinogens, parenteral tranquilizers and psychosurgery performed under local anesthesia.

2. The quantitative degree of anxiety is increased before other clinical psychiatric symptoms and signs appear.

3. The quantitative degree of anxiety must be decompressed before there is any amelioration of other clinical symptoms or signs.

4. The report shows a similarity in results using various multidisciplinary approaches.

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Effect of Surgery on Psychotic Patients

GEORGE M. DAVIES, M.D., and BUFORD H. BURCH, M.D.

While there are many reports in the literature on postoperative psychoses,[1,2,3] little is to be found on the improvement of psychotics following surgery.[4,5] This report concerns patients who have undergone chest surgery at the Patton State Hospital Tuberculosis Unit. Dramatic changes occurred in some patients immediately following surgery. The changes were temporary in one group and persisted in the other. The number of patients showing improvement, about 33%, is significant because it compares favorably with the percentage improved by such physical methods as electroshock, insulin, etc., which are designed specifically to treat psychoses.

Clinical Findings

During the last half of 1957 a total of 54 thoracotomies were done involving resection of all or part of one lung. All patients were given pentothal induction and maintained on N_2O and oxygen with endotracheal intubation. There were 49 patients with tuberculosis of the lung, two had emphysematous bullae, one primary fibrosis, one a sarcoma, and one a neurofibroma. All of the patients showing improvement were cases of pulmonary tuberculosis and were psychotic. None received special attention or treatment, nor had they received any individual psychotherapy to a significant extent prior to surgery. Of the 54 patients, 18 (33%) showed a significant degree of improvement from the moment they recovered from the effects of the anesthetic postoperatively. Two patients (4%) improved, but relapsed. Nine patients (17%) improved and maintained their improvement though they will probably remain chronic psychotics. Seven patients (12%) improved sufficiently to be discharged.

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Discussion

It is beyond the scope of this report to discuss theories of cerebral metabolism and mental function that may be responsible for the change. However, we feel that the fol-

lowing mechanisms are involved. Surgery is a form of stress causing many changes in body physiology.[6] These changes are nonspecific in that they occur regardless of the type of trauma or agent which starts the adaptation syndrome of Selye.[7] Treatments such as insulin shock, electroshock, etc., may be regarded simply as different ways to trigger the adaptation syndrome of Selye, and bring about altered physiology. Since surgery and physical methods both have stress as a common denominator, we suggest that the altered physiology brought about by stress is very likely responsible for the observed improvement.[8,9] Explanations which ignore known physiological changes occurring as a result of surgery may be given briefly as follows: patients who fear death are reassured by coming out of the experience alive;[10,11] fear, the principal emotion in any psychosis, is greatly decreased with resulting release of emotional energy which can be directed in more normal ways. The waking up of the patient postoperatively and his consciousness of severe physical pain is enough to start a chain of rational thoughts such as, "I have pain; I am a person; I've had an operation; there are people here," etc.

At this time, we are unable to predict which patients will improve mentally after surgery. All who improved had been psychotic many years, were schizophrenic, and were not believed to offer any hope of becoming leave candidates. Preoperatively, it would be hard to visualize this group of patients becoming any worse. This probably accounts for the fact that postoperatively none did become more psychotic.

Case Presentations: Reactions of the improved patients as demonstrated by speech and behavior will be described:

Case No. 1: A 45 year old schizophrenic female had been hospitalized for four years. She would behave in a silly fashion, placing plastic covers over her breasts and making comments such as, "It's a complex world we live in." She was paranoid and suspicious of other people. She had been treated for tuberculosis for many years and it was the advised surgical opinion that a left pneumonectomy would be required to give this patient an opportunity for recovery from her pulmonary disease. This operative procedure was carried out and a good result was obtained. Postoperatively the patient did not recall that she was going to have an operation or even the actual day of the procedure, and indicated that this was the reason for her lack of fear. "Maybe I was too dumb to be scared." (Lack of contact with reality.) She was reassured by objective reality, stating, "It wasn't as bad as I thought it was going to be." Insight into her problems was reflected by statements such as, "I think I have learned what's wrong. I'm willing to accept the responsibility of my illness and feel much better that my TB is corrected. There are so many things I don't understand. People are responsible sometimes, sometimes not, for what they are doing. I still don't know enough about it." This patient received no individual psychotherapy before or after surgery.

Case No. 2: A 51 year old white male, chronic schizophrenic, had been pushing and hitting other patients, throwing his urinal against the walls and uttering abusive, offensive remarks. His behavior was so completely uncontrolled that constant restraints were required. This type of behavior continued despite what was considered to be adequate administration of tranquilizers. This patient had a pulmonary resection for tuberculosis. To our surprise, as the patient awakened following his surgery, he was noticeably calm, mentally alert, and stated, "I decided it would be best for me to go ahead and have it. I've been trying to avoid having an operation; I have been walking out of hospitals for years. I am now better because I tried to cooperate instead of being so antagonistic. I was mixing myself up." The patient exhibited some weakness, complained that he could not get out of bed and expressed a desire to be tucked in bed. This mild regression was observed for approximately two weeks following surgical intervention. Following this period, he gradually began to express interest over the details of his home town, requesting papers from friends and relatives by letter. His letters became lucid, organized and friendly. This patient has made further, steady improvement.

Apropos of the belief that the altered physiologic mechanism produced by stress provides the environment in which improved cerebral function is possible, our recent experience with a young schizophrenic who quietly developed a perforated appendix is a case in point. This patient for a long period of time had been catatonic, exhibiting mute, resistive behavior prior to the development of signs and symptoms of an acute appendicitis with perforation. At the time of perforation the patient showed a dramatic change in his mental status, becoming lucid, cooperative and carrying out extended conversations which were quite normal. There was some delay in preparation of the patient for surgery since his condition was grave. Following removal of his appendix the pa-

tient maintained his mental improvement but, unfortunately, the remission did not last and the patient slipped back into his previously observed mute, catatonic state. This case suggests that as long as there was actual physiologic stress, the patient's mental behavior was improved. The necessary surgical delay makes this even more apparent. Also, as the patient began to physically recover, his mental condition began to deteriorate. This is in keeping with the subsidence of the alarm phenomenon observed and extensively discussed by Selye.

Examples of markedly disturbed patients have been cited above. Patients who were not so disturbed did not exhibit such dramatic changes, but realistic complaints about chest pains, etc., would often make their appearance. Some of the patients would begin to accept the diagnosis of pulmonary tuberculosis and, on occasion, would express a belief that surgery had indeed been necessary. We observed improvement in patients who seemed capable of trusting and relating in a friendly manner to personnel, while others exhibiting the same traits failed to improve after surgery. Fear of impending death or disaster prior to surgical intervention was present in many of those who improved, as well as in some who did not improve. Patients who exhibited verbal denial of impending surgery were found in both groups.

Conclusion

At this time we are unable to point out any psychological attitude, sex difference, age, extent of pulmonary tuberculosis or other factors to account for improvement. We have been unable to pick out any finding which would permit us to predict which patient will improve following surgical intervention. Many mechanisms can be suggested but we feel that further investigation will be far more productive than idle dissertations concerning possible mechanisms. We should like to point out that whatever the mechanism may be, if the common denominator is indeed stress brought on by surgery, it can precipitate a psychosis in the predisposed "normal" individual and also bring about a remission in the psychotic.

Summary

Following thoracic surgery for pulmonary tuberculosis in the mentally ill, approximately 33% of the patients showed a definite improvement in their mental status immediately following surgical intervention. Two patients (4%) improved but relapsed, nine patients (17%) improved but remained hospitalized, and seven patients (12%) improved sufficiently for discharge. We have been unable to predict prior to surgical intervention which patients would show a remission in their mental illness. The remission, when it occurs, is dramatic, definite and can occur without benefit of individual psychotherapy. We believe the observed remission is brought about by change in the physiologic mechanism induced by surgical stress.

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Mental Deficiency and Its Causation

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The question what causes mental deficiency cannot be answered with complete certainty, but we now know that a large number of retarded children owe their mental handicap to injuries and diseases sustained before, during and after birth.

Two large groups are usually defined: The primary and the secondary. We will define the primary group as that in which the cause is within the organism itself; in other words, it is due to heredity. A few decades ago, we thought that this group included the great majority of all cases of mental retardation. Eighty out of a hundred children were then considered to be the result of poor heredity. This group encompasses the hereditary and familial cases and certain physical anomalies frequently associated with mental retardation. Different forms of mental handicap have different forms of inheritance. Conditions responsible for low-grade mental deficiency such as phenylketonuria, microcephaly, oxycephaly, Laurence-Moon-Biedl syndrome, amaurotic family idiocy and tuberous sclerosis depend on a single gene of large, penetrating effect. On the other hand, high grade mental retardation is the frequent result of a large number of small genes of additive, cumulative effect, whilst mongolism is thought to depend upon both hereditary and environmental factors.

Genetic factors still play an important role in the causation of mental defect. It is the opinion of the writer that some 45% of all cases are primarily due to hereditary factors. On the basis of recent institutional surveys, it has been found that some 21% of individuals are mentally defective secondary to various causes arising before, during and after birth. The remaining 34% show in their histories a combination of environmental and inborn factors.

The secondary group includes the actual injuries (traumas) to the brain and various infections which may attack the unborn fetus or young child. The role of certain infectious diseases, sometimes mild ones, that affect expectant mothers, for instance, German measles, syphilis and toxoplasmosis (a protozoal infection) is well known. Most of the maternal infections that involve mother and child occur in the first three months of pregnancy, particularly between the sixth and twelfth week. Severe attacks of measles, mumps, whooping cough and scarlet fever may also result in the child becoming mentally defective. The application of therapeutic doses of x-ray or radium to the region of the hip girdle (pelvis) of an expectant woman during the early months of pregnancy may result in brain malformation and mental deficiency.

Many parents have frequently asked me to tell them something about the Rhesus factor in connection with mental retardation. Rhesus is the name of a monkey (macaca rhesus) after which a specific inheritable blood group factor, the Rhesus factor, is called. Individuals described as rhesus-positive or rhesus-negative, depend on its presence or absence in their blood. It was discovered some 16 years ago and exists in the blood of about 85 per hundred of white persons. They are the "RH positive," the rest, some 15%, being "RH negative." The trouble may arise when an expectant woman with RH-negative blood carries a child that has inherited the RH positive factor from the father. She might develop enough antibodies in her own blood to attack and destroy the RH-positive blood of her baby. This kind of blood combination (antibody-antigen reaction) occurs in some 13 per hundred of all marriages in the U.S. The group, on the whole is small, and the trouble occurs only in a few rare cases (1%). The rhesus factor may cause damage to the baby's brain, may be responsible for cerebral palsy, repeated still-births and fetal massive swellings (hydrops). Severe jaundice, liver damage and anemia complicate the clinical picture.

A diagnosis made in retrospect many years after birth presents considerable difficulty and is frequently unreliable. The criteria demanded for retrospective diagnosis varies considerably in different countries,

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different clinics and with different specialists. This undoubtedly explains the striking discrepancies in the incidence of acquired factors in the various studies which have appeared.

Birth trauma includes various injurious mechanisms, such as tearing of, and bleeding into, the brain substance, clotting of the blood in the veins and sinuses of the brain, blood cysts, both unrecognized and those unsuccessfully treated, and prolonged lack of oxygen (anoxia). In the latter condition, the cells of the brain do not get, or cannot utilize, sufficient amounts of oxygen and sugar for normal functions and this may occur in the baby before, during and after birth. Some authorities assume that anoxia is the most frequent cause of cerebral palsy and accounts for some 12% of all cases. Now, what are the conditions causing lack of oxygen to the brain? Well, there are quite a number. To enumerate only a few I should like to mention anemia in the mother, morbid conditions in the pregnant womb, kinking of the cord and the twisting of it around the baby's neck. Then there are certain disorders in the mother: Diabetes, impaired blood-circulation and toxemia of pregnancy.

All these pathological factors may result in damage to the unborn, growing brain. During the actual birth process the child may aspirate mucus or the child's lungs may collapse; breech deliveries may cause temporary diminution of blood flow to the brain, or sudden pressure changes during birth such as in precipitate labor. In the young child, the following occurrences may have a similar damaging effect on the brain. Malformations of the heart, diabetes, fall of blood sugar, exposure to a high concentration of oxygen, particularly in the case of premature babies, often resulting in blindness and all sorts of brain abnormalities. These include the tumors, cysts, etc. In summary, all conditions which interfere with the normal oxygen and food supply of the growing fetal brain may be responsible for cerebral (brain) damage.

Post-natal conditions include infectious diseases of the brain and its coverings such as encephalitis and meningitis due to various organisms that will damage the delicate nerve cells and pathways of the young brain. Those damaging toxic agents may cause impairment of the intellectual functions of the brain such as spastic paralysis of extremities, seizures or generalized stiffness of the whole body.

The unsolved problems in the field of mental retardation are numerous. The present day approach to this speciality, however, has been considerably stimulated by the positive attitude on the part of the medical profession and the public in general. New theories, investigations and laboratory tests have been evolved which are based on research and on new biochemical discoveries. Previous factors once considered hopeless, such as, congenital malformations, damage to the brain cells, metabolic disorders, have now begun to yield to new types of research methods.

The less informed observer, however, may have gained the impression that little progress has been made in the actual psycho-neurological field. This is not entirely correct, although we must admit that progress has not been as fast as we all wish it to be. We still don't know enough about the causes and prevention of mental deficiency. However, we do know more about the classification and identification of different types of mental retardation. Neurological, metabolic, X-ray, electro-encephalographic and similar studies have been helpful in the better understanding of the nature of this handicap.

Further intensive investigations are still needed. These studies will only be brought to a successful conclusion if the concerted efforts, so ably begun, are continued through close teamwork between the clinicians and the laboratory workers. Generous amounts of public funds must be set aside for research and better training methods evolved. In this respect, I believe, we may have reason to be optimistic for the future of our retarded population.

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Clinical Experience with a Meprobamate-Promazine Combination in Psychiatric Practice

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Extensive researches have been carried out for several years with the psychotropic compounds in private practice as well as in various types of institution, to establish the proper role of the agents in the general psychotherapeutic picture and to determine the most satisfactory methods for obtaining the results desired. In an effort to clarify the problem, Truitt classified the ataractic compounds into four main categories, according to chemical composition. Barsa[1] evolved a method of more practical clinical usefulness. He divides these agents into two general groups, based on the two dissimilar types of pharmacological properties they possess, as indicated by the effect on behavior: (1) Tranquilizing action (relaxation and quieting of the emotions without influence on the mental processes). (2) Antipsychotic activity (alteration of abnormal thought patterns, with suppression of hallucinations, delusions and fears). He suggested that a compound may act upon one region only in the central nervous system, or upon one area predominantly and upon others to a lesser degree. Meprobamate, a derivative of mephenesin, for example, primarily affects the interneuronal systems of the thalamus and spinal cord, thus lessens emotional reactivity. Promazine, a phenothiazine derivative, is believed to act mainly upon the reticular-activating system in the hypothalamus, thus tends to subdue disturbances of the mentality and to control motor excitation.

A number of previous clinical studies[2-8] suggested to us that certain advantages might be gained, in treatment of the neuroses and some types of psychoses, by combining meprobamate and promazine in a fixed dosage form containing a smaller volume of each than had been required for perceptible effect in previous trials.

Plan of Study: The total series of 50 patients comprised two groups—one of 35 institutionalized women (Patton State Hospital, Patton, Calif.); the second of 17 men and seven women treated in office practice. Thus, of the entire series, 29 per cent were men and 71 per cent women. The men ranged in age from 18 to 50, with an average of 33 years; the women, from 21 to 60, with an average of 37 years.

The institutionalized patients had been in the hospital, before start of treatment, for periods ranging from three days to 19 years, with an average of 2½ years.

Symptoms are listed in Table I. The commonest target symptoms (psychic or somatic) were:

1) Associated with a manic or schizophrenic type of reaction:

(a) restlessness and overactivity, 20 patients;
(b) agitated, disturbed behavior, 19 patients;
(c) delusional trends, 16 patients.

2) Associated with a depressive type of reaction, mainly involutional, 19 patients.

3) Associated with a neurotic type of reaction—fearfulness to panic reactions, 17 patients.

The various diagnostic categories are listed in Table II. Included is a diversity of schizophrenic derangements, psychoses, organic syndromes, severe character disorders and psychoneurotic disturbances. Schizophrenics were commonest in the hospitalized group (22 patients). Anxiety neurosis, with or without depression, was the most frequent diagnosis in the office-treated group (10 patients); others showed evidences of schizophrenic (6 patients) or psychotic depressive reactions (3 patients).

Medication: For the institutionalized patients the initial total daily dose ranged from two to 16 capsules. Most (30 patients) received six capsules. The dosage for the office patients ranged from three to eight

The compound used in this study was Prozine, the trademark of Wyeth Laboratories for capsules of meprobamate, 200 mg., and promazine hydrochloride, 25 mg.

capsules daily, also with an average of six capsules.

Duration of Treatment: The hospitalized group remained under medication for five to 62 days, with an average of 24 days. The office patients were treated for ten to 90 days, with an average of 50 days.

Results

Best results were obtained in the office patients—32 per cent of the target symptoms were entirely relieved; 53 per cent were significantly and 9 per cent moderately decreased, and 6 per cent were unaltered.

This group was composed mainly of patients suffering from neurotic tensions, or conversion or psychophysiologic reactions. Depressive reactions of neurotic and involutional type were also represented, as well as psychotic reactions, both manic-depressive and schizophrenic, in partial remission. The patients who responded were consistently more amenable to concurrent psychotherapy. All those in whom the depressive syndrome

TABLE I

Target Symptoms and Response to Treatment Observed in 59 Patients

(35 Institutionalized Women, 24 Men and Women in Private Practice)

Target Symptoms	No. Patients	Effect of Treatment: Unaltered	Moderately Reduced	Significantly Reduced	Eliminated
Manic Syndrome					
Restlessness	20	3*	2	8	2
Agitation	19	3*	3	11	2
Unpredictable behavior	7	1*	2	1	3
Aggressiveness, combativeness, resistance or destructiveness	6	2*	1	3	0
Increased psychomotor activity	4	1*	1	0	2
Lack of emotional control	3	0	0	3	0
Depressive Syndrome					
Emotional depression	19	0	2	14	3
Inertia	6	0	2	4	0
Insomnia	6	0	1	2	3
Suicidal tendencies	5	0	1	3	1
Self reproach	3	1*	0	1	1
Stupor	2	1*	1	0	0
Schizophrenic Syndrome					
Withdrawal from reality	8	0	4	3	1
Suspiciousness, delusional trends	16	2*	6	7	1
Hallucinations	5	0	1	2	2
Personal untidiness	3	0	2	0	1
Neurotic Syndrome					
Tension, irritability, lack of initiative	12	2*	2	5	3
Diffuse worry and anxiety	3	0	1	1	1
Inability to concentrate or work	2	1	0	0	1
Fears, panic reactions	17	1	4	9	3
Somatic complaints without organic basis, hysteria	9	3	1	4	1
Nausea	1	0	1	0	0
Pruritus ani	1	0	0	1	0
Hypertension	1	0	0	0	1
Alcohol withdrawal	2	0	0	2	0
Epilepsy					
Convulsive seizures	1	0	1	0	0
Over-all percentage response		12%	22%	46%	20%

*Institutionalized patients only.

TABLE II

Psychiatric Diagnoses in 59 Institutionalized and Office Patients

Diagnosis	Institutionalized Number	Office Number
Schizophrenic reactions:		
(a) paranoid	7	2
(b) undifferentiated	7	6
(c) catatonic	4	
(d) simple	3	
Sociopathic personality	1	
Manic-depressive psychosis	6	
Psychotic depressive reaction		3
Chronic agitated derpression	2	1
Involutional psychosis, with or without depression	1	1
Psychoneurosis with depressive reaction	1	1
Anxiety neurosis, with or without depression		10
Chronic brain syndrome	3	
	35	24

was present experienced a lift in spirits of varying degree, and were scored accordingly. Tendency to self reproach, suicidal thoughts, ertia and insomnia were relieved to some ent, or eliminated. Anxiety and tension were also lessened in the neurotic patients and the tendency to worry and panic reactions was consistently reduced. Psychologic reactions were uniformly relieved. With the general improvement in the attitude of these patients, the target symptoms were overcome or greatly decreased in the majority of cases (Table I).

In the hospitalized group, 17 per cent of the target symptoms were eliminated; 41 per cent were significantly and 27 per cent moderately alleviated, and 15 per cent were unaffected. These patients were psychotics, some of long standing, whose mental disorders had been diagnosed as schizophrenic, manic-depressive or involutional. There was also a scattering of severe psychoneurotic reactions among these cases. Tension was reduced in some degree in practically all of this group; the patients became quieter and more amenable to other therapeutic measures. They were not so restless or aggressive; the inclination to withdraw and other target symptoms were lessened. The progress of the patients in these areas was scored correspondingly.

In the over-all series, 20 per cent of target symptoms were eliminated, 46 per cent were significantly and 22 per cent moderately reduced, and 12 per cent were unaltered (Table I). Thus there was satisfactory control of symptoms, in the entire study, of 88 per cent.

Supplementary medication, usually promazine, was administered to the hyperactive and disturbed patients for initial suppression of excitement, after which maintenance with the meprobamate-promazine combination was adequate for prevention of behavior deviations. In both the hospitalized and office-treated groups, lessening of restlessness, agitation and the pressure of overactivity was a consistent finding.

Discussion

Meprobamate-promazine is particularly useful for relieving anxiety in its various clinical settings. In the neuroses, elimination of lessening of autonomic reactivity facilitates psychiatric treatment. The combination is indicated for management of the psychoneuroses when promazine in the usual dosage is not required, and also has been useful as an adjunct to anticonvulsant medication.

In our experience, the meprobamate-promazine combination is indicated for depressions in which conventional treatment, as with the amphetamines, has had little effect. Depressive reactions marked by agitation and fearfulness are satisfactorily relieved by the compound; in fact, in this study, the combination seemed to possess the qualities of an antidepressive. Alcoholics are maintained well during withdrawal and seem less liable to periods of depression which, if unrelieved, are prone to weaken their resistance to relapse.

The one hypertensive patient in this study, whose blood pressure had averaged 180 mm. Hg systolic over a period of many months, was chronically incensed and angry but unable to explain his feelings. His symptoms apparently had originated in war service. Under meprobamate-promazine medication the blood pressure returned to levels within the normal range and his behavior changed

remarkably. He slept without additional sedation and, as he expressed it, felt "like a new man." This patient is still receiving psychiatric treatment.

In control of psychotic episodes, meprobamate-promazine has been successfully used as an adjunct to other agents. For instance, a schizophrenic patient had regressed and become withdrawn during treatment with prochlorperazine alone, and had vomited nightly. On addition of meprobamate-promazine to the regimen his vomiting ceased and regression was checked although prochlorperazine was continued to control his periods of excitation.

Side Effects: No side effects developed in this series. The meprobamate-promazine capsules were tolerated well even by those known to be sensitive to chlorpromazine. The combination may be substituted for other ataraxics with no expectation of untoward effects if there is no sensitivity to meprobamate.

Summary

A combination of meprobamate and promazine in one fixed dosage form containing a smaller volume of each agent than had been required for clinical effect in previous trials was administered to a series of 59 patients, divided into two groups. One group comprised 35 institutionalized women; the other, 24 office patients. Schizophrenic derangements, psychoses, organic syndromes, severe character disorders and psychoneurotic disturbances were included in the diagnostic categories represented. The average total daily dose for both groups was six capsules of the meprobamate-promazine combination. The hospitalized patients were treated for an average of 24 days; the office patients, for an average of 50 days.

Best results were obtained in the office patients—32 per cent of target symptoms were completely, 53 per cent significantly and 9 per cent moderately relieved. In the over-all series, 88 per cent of the total symptoms were satisfactorily controlled (especially in the hospitalized patients, within the limit to be expected in the individual case). In both groups lessening of restlessness, agitation and the pressure of overactivity was a consistent finding.

The combination is particularly useful for relieving anxiety in its various clinical settings, and seems indicated for depressions in whch conventional medication has had little effect; in fact, the compound seemed to possess the qualities of an antidepressive. Meprobamate-promazine is indicated for management of the psychoneuroses, and may be used as an adjunct to other ataraxics and anticonvulsants. No side effects developed in this series.

The use of ataractic medication as an adjunct to the management of psychiatric problems is illustrated in this series. Insight and understanding of emotional problems cannot be obtained by drugs alone. However, therapy is facilitated by control of the target symptoms, as described in this report.

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Acknowledgment: The assistance of Dr. L. A. Beardsley in this study is deeply appreciated.

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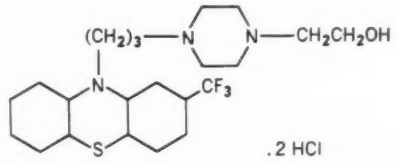
Clinical Evaluation of a New Fluorinated Phenothiazine Neuroleptic, Fluphenazine

IRVING J. TAYLOR, M.D.

Since the first reports appeared in the American literature in 1954 of the beneficial effects of chlorpromazine on severe psychomotor excitement and other psychotic symptoms,[1-4] the development of the phenothiazine compounds has advanced rapidly. Hardly has one compound been introduced before new ones are synthesized. At the present time, at least ten phenothiazine derivatives are used as neuroleptic drugs, chiefly in the treatment of psychotic patients[5] and there is a continuing effort to develop new and more potent variations of the basic phenothiazine nucleus improving therapeutic effectiveness and at the same time decreasing side reactions.

Recently a new phenothiazine compound designated as fluphenazine (Prolixin*) has been introduced for clinical investigation. In fluphenazine, a hydroxyethyl piperazine propyl side chain and a trifluoromethyl radical have been added to the phenothiazine nucleus as follows:



The resulting compound, a trifluoromethyl analog of perphenazine, is one of the most potent phenothiazine derivatives yet developed. It is shown to be approximately 25 times as potent as triflupromazine and approximately 60 times as potent as chlorpromazine in its tranquilizing effect on the monkey and in inhibiting a conditioned response in rats.[6]

In preliminary clinical studies, Darling[7] found that milligram for milligram, the therapeutic effectiveness of fluphenazine was at least 25 times that of chlorpromazine in hospitalized psychotic patients.

From Taylor Manor Hospital, Ellicott City, Md.

*Supplied by E. R. Squibb & Sons, New York, N. Y.

Over the past six months, fluphenazine has been administered to a number of patients with mental illnesses who reported to this hospital for treatment. In these trials, fluphenazine proved to be an effective tranquilizer, the most potent of any of the effective phenothiazine derivatives used by the author, with strong anti-hallucinatory and anti-delusional properties. Moreover side effects could be controlled so that the drug provided therapeutic effectiveness accompanied by a smoother clinical course than with other phenothiazines. A brief report of the results obtained with this drug follows.

Method of Study

The Patients

Since the initiation of this study on June 30, 1958, a total of 188 patients has been treated with fluphenazine; 173 were inpatients and 15 were out-patients. All were adults over 16 years old, except for three of age 14. All had psychiatric illnesses, predominantly psychotic and acute. In the majority of these patients, therapy was continued for two to three months, which is the average length of stay in our hospital. A few patients were on the drug for less than three weeks. The reasons for discontinuing therapy were varied and unrelated to the action of or reaction to the drug, being usually administrative, such as the removal from hospital against medical advice. Seven of the 188 patients have received fluphenazine since the beginning of the study, slightly over five and a half months, and are still taking the drug. Six additional patients have received fluphenazine over four months. As of February 1960 we have administered fluphenazine to over 300 patients. Many have been on the drug for one year or more.

The Medication

Total daily doses of fluphenazine ranged from 1 mg. to 10 mg., the medication being administered in the morning as a single dose in all but five patients. Doses of 5 or 10 mg.

a day were generally given to the severely agitated or acute psychotic patients. When they became convalescent, the dosage was reduced to 2.5 mg. a day.

Three patients received more than 10 mg. daily—one of these was given 20 mg. daily for two days and two others 15 mg. daily for two weeks. The average patient was given 5 mg. immediately on admission to the hospital, 5 mg. on the following morning, and 2.5 mg. each morning thereafter.

Fluphenazine was administered orally throughout the study, either as a tablet or an elixir, except in 19 cases where the drug was administered intramuscularly for the first few days of treatment and then given by mouth, or in a few cases where the drug was administered intramuscularly for up to three consecutive weeks. Intramuscular doses were 1 cc. (2.5 mg.) one to three times a day.

Other therapeutic aids such as psychotherapy, change of milieu and electroshock therapy, were used in most cases. Barbiturates were frequently given at bedtime to the patients who required aid in sleeping. In addition, those patients who were believed unable to benefit from a phenothiazine tranquilizer were excluded from the study.

Results

The results of treatment were as follows:

Clinical Response	*No. of Pts.*
Excellent, or much improved	77
Good, or improved	64
Poor, or not improved	23
Discharged before final evaluation	24
Total	188

Of the 188 patients treated with fluphenazine 141 were considered to be improved, and of these, 77 showed much improvement. In patients with psychotic symptoms a favorable change was manifested in their subjective symptoms and behavior, a more appropriate affect, and a disappearance or diminution in the intensity of their hallucinations and delusions. Improvement was evident in those patients without psychotic symptoms by a reduction in their pretreatment anxiety and tension to a point where they could function more normally.

The action of the drug was rapid—within an hour of the first dose the patient usually felt a decrease in anxiety. The action of the drug was sustained—a single dose in the morning was usually adequate to prevent a breakthrough of symptoms for the next 24 hours. Because of its rapid action, there was little need for the intramuscular administration of fluphenazine except in patients who refused oral medication. The sustained action of the medication had distinct advantages. Around-the-clock therapeutic effect could be maintained with one or two doses in 24 hours, and in most instances, with a single dose. This single dose was not only convenient for the nurses giving the medication but also for the patient.

No difficulties were encountered when electroshock therapy or barbiturates were administered concomitantly with fluphenazine. No advantage was apparent in giving more than a single dose of fluphenazine as a satisfactory clinical response was achieved and maintained on a regimen of one dose daily. There appeared to be no advantage in exceeding a daily dosage of 5 mg. of the drug.

Side reactions were conspicuous by their absence and, except for extrapyramidal effects in some patients who received more than 5 mg. of the drug each day, there were no untoward reactions. There was neither drowsiness nor lethargy and none of the usual autonomic nervous system reactions to other phenothiazines, such as blurred vision and dryness of the mouth. Patients receiving 1 mg. of the drug each day felt nothing and most of those receiving 2.5 mg. a day were unaware that they had received active medication. Yet 2.5 mg. daily was the most effective dose of fluphenazine in the average case. About half of the patients who received 5 mg. of the drug each morning developed some extrapyramidal dystonia manifested principally by spasm of the muscles of the neck and shoulder girdle and rarely, by a feeling of weakness in the muscles of the leg. These symptoms were especially prominent in patients receiving 10 mg. daily but could be dispelled by reducing the daily dosage to 5 mg., or to 2.5 mg., and if the symptoms were severe, by omitting medi cation for a day or two then resuming it i reduced dosage.

Clinical Examples

A brief description of three representative patients will illustrate the clinical response to fluphenazine:

Case 1. A female, single, 25 years old, was referred to the hospital for consultation and possible admission because of her emotional panic which was heightened by thoughts of suicide.

Although this patient was cooperative and not physically agitated during the interview, she exhibited intense apprehension by a shakiness in her voice and a tremor of her entire body. She expressed the feeling that she was going to explode from inner tension. As her problems were discussed with her, the apprehension began to subside and she subjectively felt much better but there remained considerable inner tension and tremor. Fluphenazine (2.5 mg.) was given orally immediately, repeated at 12-hour intervals for two doses, and then one dose was given every 24 hours. Since the patient no longer appeared to be an acute suicidal risk, she was sent home after the consultation and instructed to telephone the psychiatrist in three hours and again each day thereafter. Within two hours after the first dose of fluphenazine, the patient experienced complete relaxation with the disappearance of tension and shakiness. The next day she was comfortable enough to return to her job. By continuing fluphenazine as directed with brief psychotherapeutic support on the telephone every day for several days, she was able to maintain her effectiveness at her job.

Case 2. A 35-year-old accountant with schizophrenia, paranoid type, had received treatment since 1949 with periods of remission on three different occasions. In March, 1955, his paranoid ideation recurred and he sought help from the F.B.I. He was treated on an outpatient basis with chlorpromazine, 300 mg. initially, subsequently raised to 600 mg./day before his delusions disappeared and later reduced to 400 mg./day on which he was maintained for two years. Any attempt to reduce the dosage or to substitute another tranquilizer for the chlorpromazine resulted in a return of symptoms. Because of a feeling of lethargy which interfered with his work, the dosage of chlorpromazine was reduced to 200 mg. as a single dose at bedtime. Though he had occasional delusions during the day he could continue to work and to live with his family. In March, 1959, fluphenazine (2.5 mg. each morning) was substituted for chlorpromazine. His lethargy disappeared, in fact he became rather elated, but his delusions did not recur. Since he was not sleeping well and his wife became alarmed at the change in his personality, 100 mg. of chlorpromazine at bedtime was added to the regimen. The patient adjusted well and was continued on fluphenazine and chlorpromazine for a month when the chlorpromazine was discontinued. During the past month he has remained asymptomatic on fluphenazine alone, 2.5 mg. each morning.

Case 3. A 44-year-old widow with a history dating to 1950 of addiction to alcohol and occasionally elixir of terpin hydrate and codeine. Since her admission to this hospital on Friday 16, 1957, she has been treated with various tranquilizers and has been allowed home visits, some going well but others ending in drinking. On July 30, 1958, fluphenazine was substituted for trifluoperazine which she was then taking. The tranquilizing effect from 5 mg. of fluphenazine each morning was the same, both subjectively and objectively, as that obtained with 15 mg. (in divided doses) of trifluoperazine daily. Under continued treatment with fluphenazine her course in hospital was uneventful until her dischage on January 15, 1959, since which time she has been continued as an out-patient on 2.5 mg. of fluphenazine each morning. By reviewing the dosages of past phenothiazines administered to this patient, their relative effectiveness, in her case on a weight basis, can be compared. The dosage ranges were.

Perphenazine—24 to 64 mg. daily.
Chlorpromazine—300 to 1200 mg. daily.
Thiopropazate—40 mg. daily.
Trifluoperazine—10 to 15 mg daily by intramuscular administration.
Trifluoperazine—10 to 20 mg. daily by oral administration.
Fluphenazine—5 mg. daily, once a day.

With the exception of fluphenazine, each of the drugs was given in divided doses.

Discussion

The findings of this study indicate that fluphenazine is an effective tranquilizer in that it has strong anti-psychotic (anti-hallucinatory and anti-delusional) properties and at the same time diminishes tension and anxiety in patients without psychotic symptoms. The rapid action of the drug is advantageous particularly in those patients who would benefit from prompt relief of anxiety and other symptoms. The sustained action of the drug is a distinct advantage in that a single dose generally sufficies for the entire day. In addition to the convenience of the single dose, there is less chance of the patient's forgetting the medication, if an outpatient.

Fluphenazine is the most potent phenothiazine derivative that has been employed at this hospital to date. On the basis of the results obtained here with each of the respective drugs, fluphenazine was twice to four times as potent, milligram for milligram, as trifluoperazine and approximately 40 times as potent as chlorpromazine.

With both fluphenazine and trifluoperazine, however, the threrapeutic range is very narrow as compared to other phenothiazines and the doctor must know precisely how to handle the dosage. On too small a dosage (1 mg. of either daily) the patient usually shows no response, while on too high a dosage (more than 15 mg. of trifluoperazine or 5 mg. of fluphenazine, daily) the patient is prone to extrapyramidal effects. Though these reactions rarely endanger life and quickly respond to anti-Parkinson medication, they are extremely disturbing to the patient who may refuse further medication, or if he is an out-patient, they may cause considerable alarm to his family.

Although high potency is an advantage since smaller dosage required to produce the desired therapeutic effect with consequent less side reaction, the most potent tranquilizer may not in all cases be the most efficient one. For example, unlike trifluoperazine or fluphenazine, chlorpromazine and triflupromazine induce a moderate drowsiness or hypnotic effect, depending on the dosage administered. While this side effect may be undesirible in the ambulatory or working patient, it is of definite benefit in the acutely agitated hospilalized patient who requires rest and eyt must be aroused for meals and other bodily needs. As with the selection of any medication, common sense must exercised in the choice of the proper tranquilizing agent.

Summary

Fluphenazine was employed in the treatment of 188 patients with psychiatric illnesses, 173 being treated in hospital and 15 on an out-patient basis. Total daily doses were 1 mg. to 10 mg., with the average dose being 5 mg. immediately on admission to hospital, 5 mg. on the following morning and 2.5 mg. each morning thereafter. Therapy was continued in the majority of cases for two or three months. A total of 141 (85.9%) of the 164 *evaluated* patients improved, with 77 of the 141 being considered much improved. Within an hour of the first dose, the patients felt less anxious and one dose in the morning was usually adequate to prevent a breakthrough of symptoms for the following 24 hours. Except for extrapyramidal effects, such as spasm of the muscles of the neck or shoulder girdle, in some patients who received more than 5 mg. of the drug each day, there were no untoward reactions. These signs were especially prominent in patients receiving 10 mg. per day but could be controlled by reducing the dosage. No drowsiness, lethargy, blurred vision or dryness of the mouth were observed. Patients receiving one mg. of the drug each day experienced no reaction, and most of those receiving 2.5 mg. a day were unaware of the action of the drug. Yet this was the most effective dose.

Fluphenazine is an effective neuroleptic with strong anti-hallucinatory and anti-delusional properties in patients with psychotic symptoms and with prompt alleviation of anxiety and tension in patients without psychotic symptoms. Fluphenazine is the most potent of the phenothiazine compounds which has been employed at this hospital to date.

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Book Review

RORSCHACH INTRODUCTORY MANUAL by George A. Ulett, B.A., M.S., M.D., Ph.D. Bardgett Printing & Publishing Co., St. Louis. 45 p.

This manual is noteworthy from the standpoint of the simplicity of presentation. Despite its brevity, it is a surprisingly complete and well organized work. The author sets out to provide psychiatrists with a convenient way of gaining some general familiarity with the Rorschach test and of effectively bridging the communication gap between psychiatry and clinical psychology. This introductory manual should be of help in these regards. Whether it will permit a person not trained in the technique to administer, score and interpret a Rorschach test is going to be a matter of opinion. The author does present some very novel and cleverly designed "interpretive" diagrams, but a neophyte confronted with them, with double and triple determinants, would be a bit hard pressed to use them with any validity. As an introduction to an understanding of Rorschach theories and principles, per se, it is an excellent contribution.

Dr. Ulett is to be commended for the restraint and judiciousness he exercises throughout in his statement about the tests. He succinctly points up the importance of clinical experience in Rorschach interpretations and he cautions the reader about the dangers inherent in a mechanical sign approach to diagnosis. Time and again he appropriately underscores the global nature of the instrument and the interrelationships between score and categories. The reader is apprised of unresolved interpretive issues and given a meaningful, if rather elementary, eclectic frame of reference.

Naturally, the manual could benefit from more extensive material in many phases, such as "testing the limits" procedure, etc. Also, a few other books might be placed in his list of references. However, the good points of this manual outweigh any shortcomings and it can be warmly recommended to those interested in facilitating a general acquaintanceship with the Rorschach.

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